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SCHISTOSOMIASIS JAPONICA: ITS CLINICAL DEVELOPMENT AND RECOGNITION *

By ERNEST CARROLL FAUST, *New Orleans, Louisiana*

SCHISTOSOMIASIS japonica was first recognized clinically almost 100 years ago in Japan, under the name Katayama disease.[1] Fifty-seven years were to pass before the etiological agent was discovered to be a trematode, which was named *Schistosoma japonicum*.[2] This oriental disease was found to be related to vesical schistosomiasis, the so-called bilharziasis of Egypt, and to be even more closely akin to Manson's schistosomiasis of Africa and of certain tropical areas in the Western Hemisphere. Ten years after the etiology of the disease had been established, it was demonstrated that the life cycle of the parasite, like that of all other trematodes, involves a mollusc, in this case a small, amphibious fresh-water snail.[3] Man and other susceptible mammals acquired the infection from wading, bathing or washing clothes in fresh water which was infested with the fork-tailed cercaria, the larval stage of the parasite that escapes from the snail. The snail, in turn, had become infected from the ciliated larvae which hatched from eggs of the parasite after the mammalian host's stools had reached fresh water.[3, 4, 5]

In addition to five relatively small endemic foci in Japan, schistosomiasis japonica was found to constitute a major disease hazard in China, including practically the entire Yangtze watershed and most of the coastal river valleys south of Shanghai.[5] Later it was discovered to be present in a small area in Formosa,[5] to be endemic on four of the larger islands of the Philippine Archipelago[6] and to exist in at least one small area in Celebes.[7] Nowhere else in the world has the disease been demonstrated to be indigenous, most probably because the appropriate snails are established only in certain countries bordering on the China Sea.

Japanese physicians in endemic areas studied patients who almost without exception were repeatedly exposed to infection from early childhood to middle

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From the Department of Tropical Medicine, Tulane University, and Commission on Schistosomiasis, Commission on Tropical Diseases, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

life or later. They suffered from hepatomegaly [8] or hepatic cirrhosis,[9] frequently with marked ascites [10]; splenomegaly,[8] anemia,[11] appendicitis [12] and at times Jacksonian epilepsy.[13] Postmortem examination demonstrated extensive granulomata of the bowel; nodular periportal fibrotic lesions and pipe-stem cirrhosis of the liver; an enlarged, firm, at times fibrotic spleen; granulomata of the brain, and occasional carcinoma of the liver or colon. In a few American and European patients in China, who were observed within a few weeks to months after a single, or at most only a few contacts with infested water, the cardinal symptoms and signs of the disease were urticaria, angioneurotic edema, an evening rise in temperature, eosinophilia and dysentery.[14, 15, 16, 17, 18] On the other hand, Chinese patients with multiple exposure, who consulted Western practitioners late in the disease, had symptoms of advanced intestinal disorders and hepatic cirrhosis.[19] Similar findings of chronic infection were reported by internists, surgeons and pathologists in the Philippines.[20]

Schistosomiasis japonica has until recently been almost a medical curiosity to all American physicians except those who have practiced in endemic areas in China. However, several years ago Bovaird and Cecil [21] studied two cases in New York, one a Japanese who came to necropsy and one an American youth who had contracted the disease in the Yangtze Valley, China. Even schistosomiasis mansoni, which parasitizes approximately 10 per cent of the population of Puerto Rico, has been relatively unknown to the medical profession in the United States.

When American military forces invaded Leyte, P. I., on October 20, 1944, they established beachheads on the East Shore and in the Leyte Valley, possibly the most highly endemic center of schistosomiasis in the Orient. Medical and sanitary officers were cognizant of the dangers of the disease and the way in which it is contracted but at the time the known ways of guarding against exposure were for the most part impractical, particularly for certain engineering companies who were under orders to rebuild bridges over the several rivers which empty into Leyte Gulf. During a period of approximately four to five months following invasion day a considerable number of troops, including both combat and service forces, acquired the infection. Some of the men developed very heavy infection, more were suffering from a moderately severe variety of the disease, while probably the largest number of all had mild symptoms or were temporarily asymptomatic. A year after the first exposure more than 1000 cases had been studied in Army General Hospitals in the United States, and the guess is ventured that a considerably larger group have thus far escaped diagnosis.

Many of the service men who may have been exposed on Leyte before control measures became effective have already been discharged from the armed forces and have resumed their place in civilian life. It is possible that some of these men may eventually develop symptoms and require a physician's care. Thus, it is a matter of concern that physicians in Veterans Facilities or in civilian practice be acquainted with the usual train of

symptoms and potential sequelae attendant on infection with *Schistosoma japonicum.*

The Pathogenesis of Schistosomiasis Japonica

An understanding of the clinical manifestations of schistosomiasis requires basic knowledge of the pathogenesis of the disease from the time of exposure until the chronic stage has developed. Whenever the small but energetic fork-tailed larvae of *Schistosoma japonicum, S. mansoni* or *S. haematobium* come in contact with human skin, as the water drains off or begins to evaporate the larvae drop their tails and start to bore and digest their way into the epidermis. Within a few minutes they are safely under the skin's surface but require several hours to burrow down to the cutaneous blood capillaries, which they enter between the sixteenth and twentieth hour. Unless they are temporarily trapped in cutaneous lymph nodes they produce very little tissue reaction (figure 1).

The young worms are passively transported through the chambers of the right heart to the pulmonary arterioles. Unlike hookworm larvae they proceed to squeeze through the capillary net-work into the venules and thence are transported through the left side of the heart into the systemic arterial circulation. A period of approximately four days is required for passage through the lungs, during which time considerable eosinophilic, epithelioid and giant cell reaction is called forth immediately around the paths of migration (figure 2). Furthermore, some larvae break out of the pulmonary capillaries and arrive at blind ends in the tissues. In addition to producing petechial hemorrhage they disintegrate and provoke an acute cellular infiltration.

Most of the larvae which reach the arch of the aorta are carried through the thoracic artery into the abdomen, although some may enter the carotids and the arteries supplying the upper part of the trunk. Only those survive which reach the mesenteric artery and pass through the capillaries into the portal vein. They apparently feed for the first time after their arrival in the mesenteric-portal blood, which is rich in glucose. All larvae which are filtered out in other capillaries become foreign-body emboli and set up both local and systemic reactions. At each site of infiltration a minute miliary lesion develops as a result of the presence of foreign protein. The degree of this reaction depends both on the amount of initial exposure and on the reactivity of the individual who has become infected.

On reaching the portal vein the microscopic larvae pass into the intrahepatic portion of the vessel, where they feed on whole blood and grow for approximately 16 days. During this period they are discharging an increasing amount of metabolites which cause an acute local inflammatory reaction in the liver and a general systemic reaction.

Now the adolescent worms begin to migrate out to the smaller mesenteric veins. *Schistosoma japonicum* proceeds for the most part to the intestinal wall drained by the superior mesenteric vein; *S. mansoni* to the lower

PLATE I

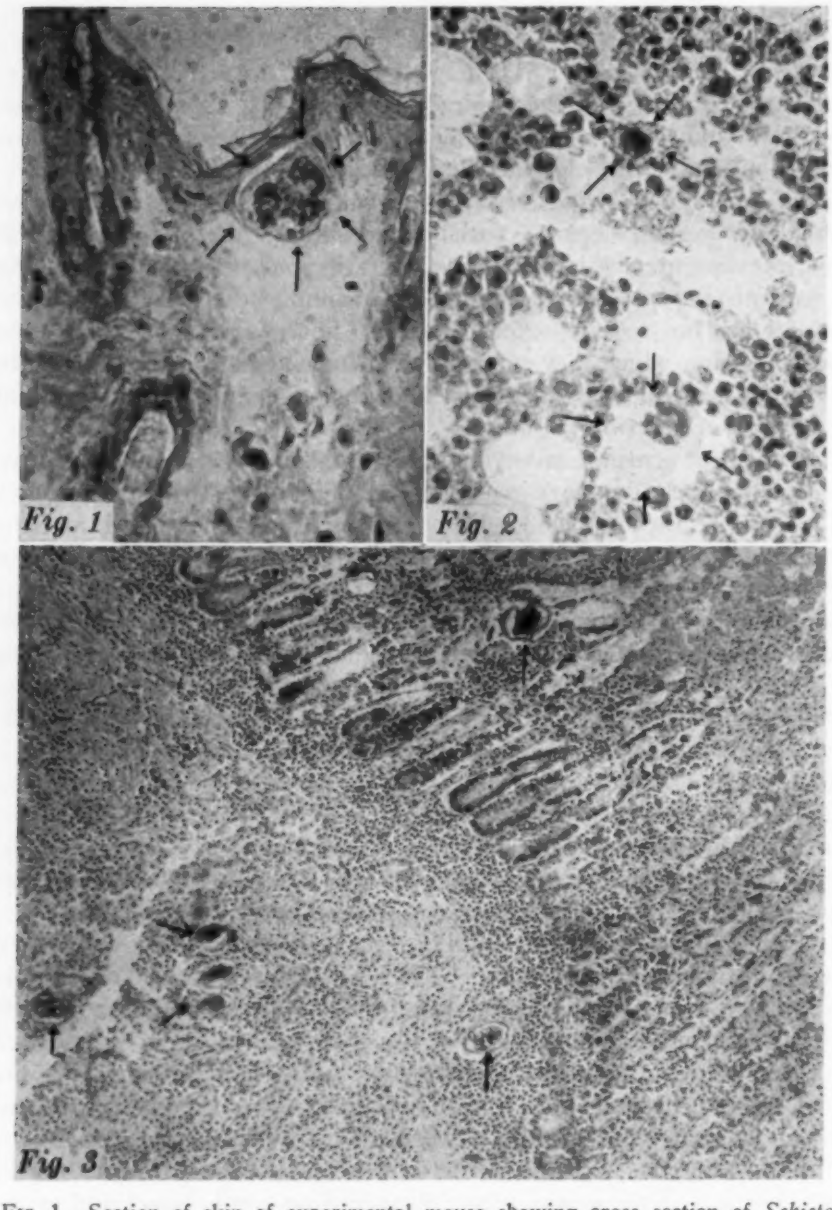


FIG. 1. Section of skin of experimental mouse showing cross section of *Schistosoma* cercaria which has penetrated under epidermis en route to cutaneous venules. Note absence of tissue reaction. × 400. (Original.)

FIG. 2. Section of lung of experimental rabbit showing pulmonary capillary and alveoli five days after exposure to *Schistosoma* infection. The migrating larvae have probably already passed into systemic circulation. Note infiltration of eosinophiles and two giant cells near the capillary. × 400. (Original.)

FIG. 3. Eggs of *Schistosoma japonicum* filtering through submucous and mucous coats of the colon. Section from postmortem of American soldier who had been exposed to infection approximately three months previously. Note mechanical damage but relatively mild tissue reaction. × 83. (Original.)

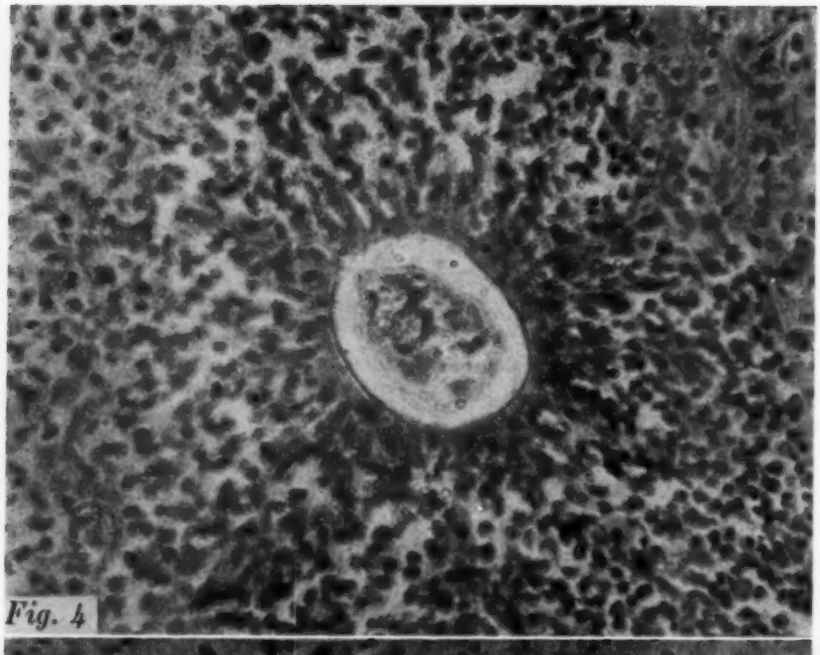
branches of the superior mesenteric and the branches of the inferior mesenteric vein, and *S. haematobium* through the inferior mesenteric and the pudendal or hemorrhoidal anastomoses to the vesicle venules. The time involved for these migrations is roughly related to the respective distances from the intrahepatic portal vessel: for *S. japonicum* this requires from one to two weeks; for *S. mansoni*, three to four weeks, and for *S. haematobium*, seven to nine weeks. Soon after their arrival in the sites of choice the worms become sexually mature, mate and the females are ready to oviposit.

Egg-laying is accomplished while the delicate female, with her anterior end directed towards a capillary, is held in position in a venule by a male. The egg is considerably larger than the normal diameter of a small venule, so that several eggs typically layed one behind another cause a distention at each site where an egg becomes lodged, with intermediate constrictions between the eggs. Thus, congestion of blood occurs in the capillaries and arterioles blocked by the eggs. Complete embryonation occurs within a short time after the eggs are deposited. Each egg now contains a ciliated larva which is already secreting a viscous lytic fluid that oozes through minute pores in the egg shell and on contact weakens the wall of the venule. The congestion of blood in the capillaries and arterioles and the digestive ferment secreted through the egg shell, together with the characteristic muscular contraction of the wall of the intestine (or bladder), combine to cause rupture of the blood vessel and escape of the eggs in small pools of blood. Before long a considerable proportion of these eggs are filtering through to the lumen of the intestine (or bladder) (figure 3), to be evacuated in a dysenteric stool (*S. japonicum*, *S. mansoni*) or in small flecks of blood and cellular detritus in the urine (*S. haematobium*).

Egg-laying continues unabated during the long life span of the worms. Before many weeks have elapsed some of the eggs have become temporarily lodged in the submucous and muscular coats of the organ, with the development of an enveloping pseudo-abscess, which at times may be expelled from the bowel wall *in toto* but more frequently becomes transformed into a pseudo-tubercle. Soon thereafter in schistosomiasis mansoni, and to an even greater extent in schistosomiasis japonica, some eggs escape into the larger mesenteric venules. These are carried into the liver, where they filter out periportally and soon become centers for pseudo-tubercle formation (figure 4). Others are diverted into collateral venus circulation and may reach the lungs, where they provoke similar tissue reaction (figure 5); or they may get out of the closed venous circulation and come to lodge in cutaneous arterioles (figure 6) or in cerebral vessels (figure 7).

In a few months thousands of eggs may be deposited by a single female *Schistosoma japonicum*. More and more they are permanently trapped in the tissues and become centers of fibrous encapsulation. As a result the intestine loses its vital tissues and develops papillomata and cicatrices, and the liver becomes transformed from an enlarged, inflamed organ into one with periportal fibrosis. With increased embarrassment of blood flow

PLATE II



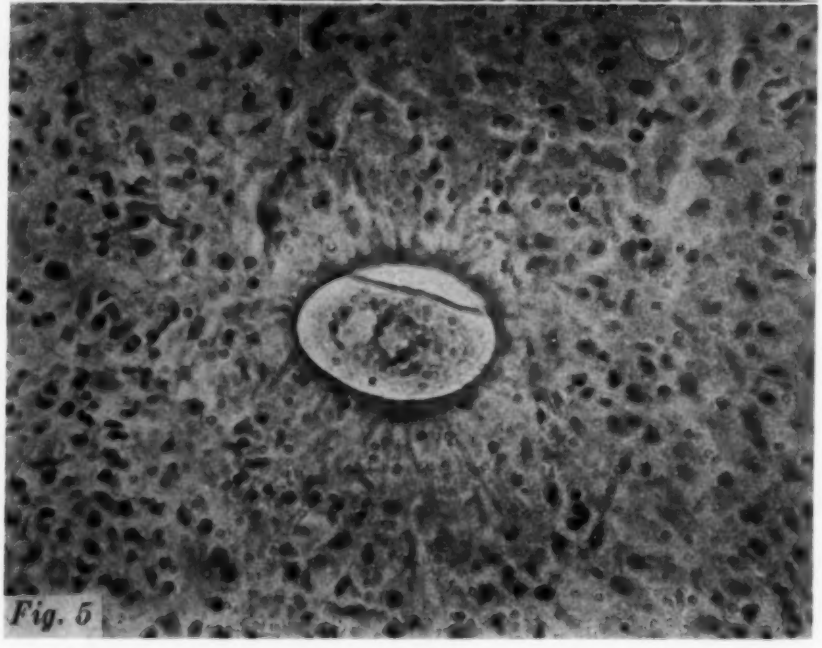
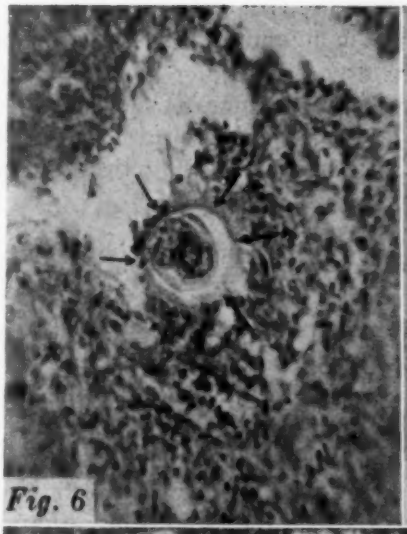


FIG. 4. Egg of *S. japonicum* containing mature larva which has infiltrated periportally into liver tissue. Note rays of mucoid material which has been secreted by larva and is exuding through the egg shell, together with inflammatory reaction around egg. From the same case as figure 3. × 300. (Original.)

FIG. 5. Egg of *S. japonicum* containing mature larva which has infiltrated from a pulmonary arteriole into the parenchyma. Note streaming rays of mucoid material and cellular reaction around egg. From the same case as figure 3. × 400. (Original.)

PLATE III



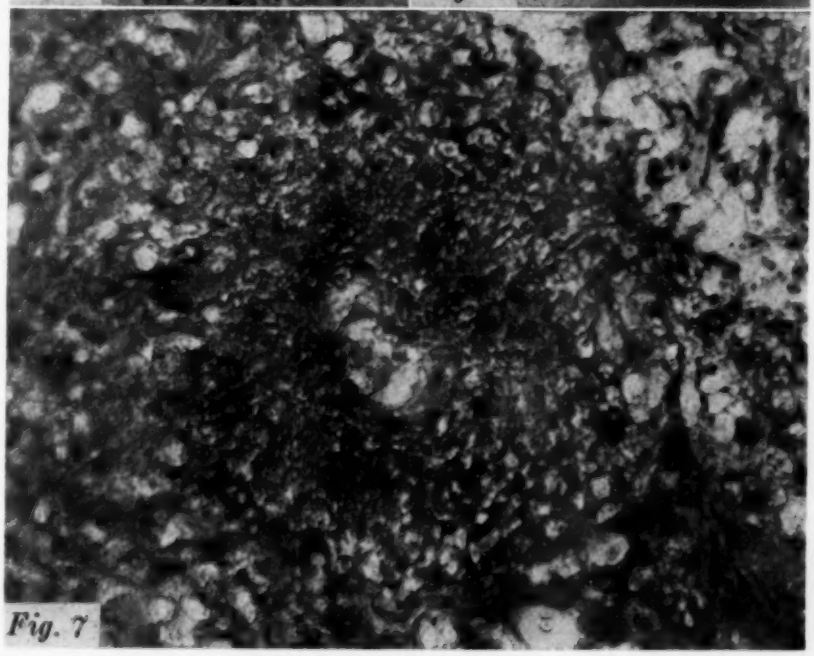


FIG. 6. Egg of *S. japonicum* which has escaped from a cutaneous intercostal arteriole, with marked cellular infiltration into the area. × 200. (Photomicrograph from section of biopsied specimen, courtesy of Major H. M. Fishbon, M. C.)

FIG. 7. Pseudotubercle formation around egg of *S. japonicum* in granuloma removed surgically from right temporo-parietal area of patient who had been exposed on Leyte, P. I. Mallory stain. × 400. (Original from section provided through courtesy of Major I. Joshua Spiegel, M. C.)

FIG. 8. Mature viable egg of *S. japonicum* recovered from stool of patient on Leyte, P. I. × 450. (Photograph by 3rd Photographic Unit, Army Medical Museum for the Commission on Schistosomiasis.)

through the liver an attempt is made to care for the return of visceral blood through collateral circulation. The spleen becomes passively congested, increases greatly in size and develops a certain amount of fibrosis. The superficial abdominal veins also become greatly distended, while in many late chronic cases ascites results. The increase in the mass of the intestines and the spleen pushes the diaphragm upwards and decreases intrathoracic volume. The lesions resulting from malnutrition and systemic intoxication become increasingly prominent.

The Developing Symptoms and Signs in Schistosomiasis Japonica

During the biological incubation period, from the entry of the larval worms into the skin until they have matured and egg-laying is about to begin, the symptoms and signs of the disease are due primarily to the intimate contact of the parasites and their metabolites with the tissues in the immediate vicinity of the blood vessels through which the worms are migrating or in which they are temporarily lodged. In addition, the systemic absorption of the by-products account for the more generalized allergic manifestations.

A needling local pain may or may not attend the rapid penetration of the microscopic organisms into the skin but there is seldom an associated dermatitis. During the somewhat longer period when the larvae are squeezing through the pulmonary capillaries, and presumably even to a greater degree when some of them escape into the alveoli, there is bronchial irritation, with an unproductive cough or at times with a discharge of small flecks of dry mucus. There appears to be no special symptom associated with the passage of the larvae through the mesenteric capillaries but those which become lodged as foreign protein emboli in other viscera may be responsible for a relatively early urticaria.

The growing worms in the intrahepatic portal vessel gradually produce inflammation of the liver, with resultant pain in the upper right abdominal quadrant under the costal margin. About the third or fourth week following exposure this organ typically becomes palpable on deep inspiration and pressure over the area elicits acute pain. Meanwhile the adolescent worms are migrating towards the bowel wall and their activity causes a feeling of general abdominal fullness and discomfort. The irritation to the intestinal wall produces a mucus diarrhea which is prodromal to the symptoms initiated by egg deposition. In this terminal stage of the incubation period by-products of the parasites are swept back in portal blood into the liver, which now becomes more acutely tender and continues to increase in size. It is firm but has a smooth surface and rather sharp edges.

The systemic manifestations during the latter part of the incubation period are those resulting from the cumulative absorption of the worms' metabolites. There are gradually increasing malaise, anorexia, nausea and possibly vomiting. Rather frequently stiffness and aching develop in the joints and muscles, or along nerve tracts, especially in the region of the neck, back and legs. The patient may wake up in the morning with intense

giant urticaria, an associated edema involving the subcutaneous tissues and mucus membranes, or with a suggestion of angioneurotic edema, whereas the night before there had been no evidence of an allergic condition. Moreover, dermatographia is relatively characteristic at this time. Transient areas of dullness and râles in the lungs, due to local edema, are revealed by percussion and auscultation. Also characteristically there is an elevation of temperature late every afternoon, a drenching sweat during the night and an afebrile but weakened state the next morning. For the first time the patient realizes that he is really sick.

Blood studies at this stage will show no essential change in the red cells but usually a leukocytosis with conspicuous eosinophilia.

The type of case which has been used as an illustration is that of an average adult with moderately heavy, single exposure. Much of the data relating to the earlier part of this stage have been obtained from questioning patients somewhat later in the disease, since they are not likely to have symptoms sufficiently severe to consult a physician until the prodromal period arrives or the acute stage is precipitated. Moreover, a physician is not apt to suspect schistosomiasis during this period unless he has had considerable experience in an endemic area. He is much more likely to consider amebiasis, malaria or infectious hepatitis as possible diagnoses. Even if a diagnosis of schistosomiasis is entertained, it cannot be confirmed until eggs are recovered from the stool.

Several successive exposures or a single massive exposure have probably accounted for the few fulminating infections in American military personnel which have ended fatally. On the other hand, infection may be so light as to be undetected clinically during the earlier stages and may be picked up only after careful stool examination or following some complication.

The second period in the disease is ushered in with egg deposition, which usually begins four to six weeks after exposure. The local and systemic manifestations resulting from irritation caused by the worms and their metabolites continue unabated. Now, however, the irritating effects of the eggs assume the leading rôle as they escape from the venules and filter into the intestinal canal. Traumatic injury to the entire bowel wall, especially the ileum and cecum, provokes hyperperistalsis and tenesmus. The stool may contain more blood and mucus than fecal material, may be unformed and jelly-like in consistency or it may be formed with streaks or clumps of blood and mucus on the outside of the feces. The entire bowel is usually painful and tender. Frequently the appetite and digestion are poor. The patient now experiences considerable loss in weight and his quotidian evening fever persists. He is acutely ill and is compelled to take to his bed.

Physical examination reveals a liver which extends several fingers below the costal margin and a spleen which has become palpable. After complete rest from two to three weeks or longer the patient feels much better and his fever has at least partially subsided. However, when he gets up and

attempts physical exertion the intestinal lesions break down and an exacerbation of acute symptoms occurs.

Throughout this period there is a continued leukocytosis with pronounced eosinophilia, at times as much as 90 per cent of the total white count. If the dysentery has been a prominent symptom, some degree of anemia may be expected.

Patients with moderate exposure may begin to exhibit abdominal tenderness and pain almost as soon as do the more heavily infected ones, but more frequently these symptoms are slower in developing in the lightly infected individuals and may reach clinical grade as late as 10 to 12 weeks or more after exposure. On the other hand, there is some indication that certain individuals with rather mild exposures may react out of all proportion to the number of worms which they harbor, while others with a relatively heavy worm burden have surprisingly mild manifestations.

During this active stage the disease can be diagnosed by the recovery and demonstration of the characteristic eggs (figure 8), which are unequally distributed in the stool and are most likely to be found in masses of blood-tinged mucus. Even though each female worm of *Schistosoma japonicum* lays many more eggs per day than does *S. mansoni*, these eggs may be too few to detect by direct fecal films, so that concentration technics must be employed. Members of the Commission on Schistomiasis of the Surgeon General's Office [22] have found that sedimentation of five-gram amounts of stool in 0.5 per cent glycerinated water, followed by the examination of three cover-glass preparations of the sediment, provides a high degree of assurance of egg recovery from stool specimens containing very few eggs.

In addition to stool examination, pinpoint nodules or distended blood capillaries may at times be visualized by proctoscopy just above the junction of the sigmoid colon and rectum. Removal of specimens of these lesions for direct microscopic observation or section (figure 9) at times provides valuable confirmatory evidence of the disease and occasionally is positive when stool examination is negative.[22]

The chronic stage of the disease is already well under way before the active period of egg extrusion subsides. Thus the symptoms resulting from fibrosis are gradually developing while the patient is still suffering from acute inflammation of the liver, diarrhea or dysentery and systemic intoxication. Gradually, almost imperceptibly, the liver begins to shrink as the miliary fibrotic processes around infiltrated eggs increase in numbers. On physical examination the organ feels hard and usually has millet-seed nodules on its surface. Pressure evokes less pain than at an early stage.

The greatly enlarged spleen, which may extend to the umbilicus or into the lower right abdomen, is firm and exquisitely tender. There is considerable thickening of the coils of the small bowel, while the transverse colon gives the impression of irregular enlargement and thickening. As a result of the infiltration of eggs into mesenteric lymph nodes, there may be a

PLATE IV

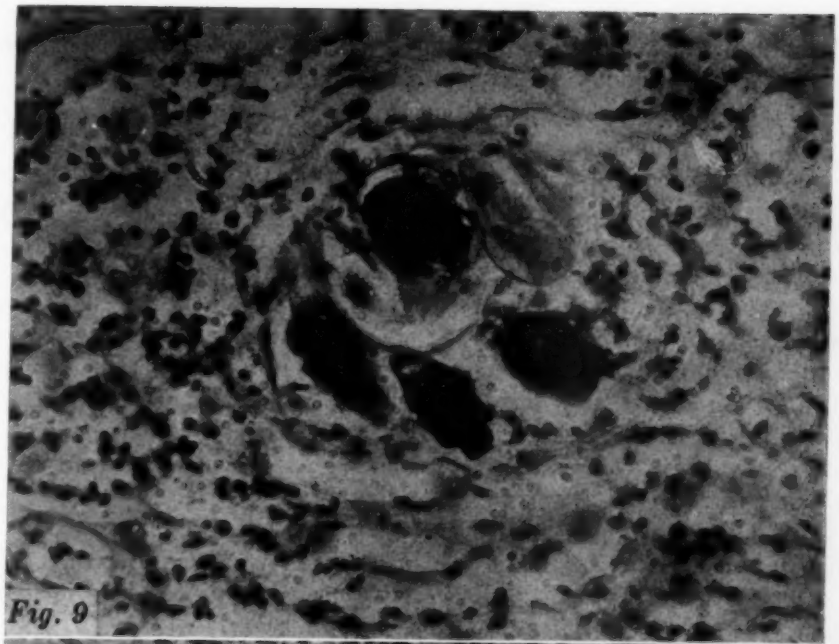


Fig. 9

Fig. 10

FIG. 9. Nest of *S. japonicum* eggs in section of biopsied nodule from sigmoid colon. × 400. (Original from section provided through courtesy of Lt. Col. Stuart W. Lippincott, M. C.)

FIG. 10. Shell of *S. japonicum* egg and active foreign body reaction in section from cerebellar granuloma removed post mortem from American veteran. × 400. (Original from material provided through courtesy of Dr. W. L. McNamara, Elmhurst, Illinois.)

mesenteric binding which tends to separate the abdominal viscera into an upper and lower portion. The greatly increased abdominal mass pushes the diaphragm upwards, with corresponding decrease in the size of the pleural cavity. Moreover, some reduction in pulmonary function probably results from the infiltration of eggs in the pulmonary parenchyma. On slight exertion there is pronounced dyspnea.

Generalized abdominal discomfort together with increased digestive dysfunction provides the basis for the dyspeptic condition and the asthenic state. Because of fibrotic scarring of the colon, intestinal stenosis or the development of papillomata, the function of the large bowel is greatly impaired. The elimination of feces becomes irregular, with alternating constipation and diarrhea. At times the infiltration of eggs in the wall of the appendix may provoke an acute appendicitis. Rarely there may be prolapsus recti. Carcinoma of the liver or rectum occasionally develops. Portal obstruction, due to stenosis in the portal venous circulation or to the presence of masses of parent worms which become lodged in a main afferent branch, results in ascites.

During this chronic stage the blood picture shows a decrease in the number of neutrophiles. There is usually a persistent eosinophilia, and a characteristic lymphocytosis. Some degree of anemia is now invariably present.

This portrayal of the chronic stage is again that of the average patient. Natives in endemic areas usually give a history of multiple exposures, so that it is difficult to distinguish between those of their symptoms which are due to chronic lesions and those of more recent origin. In any case the advanced chronic condition may be expected to develop in about five years or less after first exposure. If the infection is light the complaints of the patient may be restricted to vague abdominal discomfort and digestive upsets, which are precipitated by physical exertion, alternating with periods of moderate quiescence. In general, it may be stated that for the same amount of infection the symptoms are more severe in schistosomiasis japonica than they are in schistosomiasis mansoni and that clinical evidence of chronicity develops considerably earlier in the former infection.

Diagnosis of the chronic stage of the disease lies specifically in the same methods as are employed for the acute stage, namely recovery of the eggs. However, the eggs evacuated in the stool at this stage are fewer in number, are discharged with less regularity and are frequently immature or degenerate. Laboratory examination should always include sedimentation of at least one stool specimen.[23] Probably proctoscopic biopsy will be even more useful now than during the earlier stage of the disease. The intradermal reaction with schistosome antigen should be positive,[22] while tests demonstrating increased serum globulin will add strong presumptive evidence of schistosomiasis. Clinically the condition must be differentiated from hepatic cirrhosis of other etiologies.

Complications Resulting from the Lodgment of Schistosoma Eggs in Ectopic Foci

In the Japanese literature on schistosomiasis there are numerous references to neurological complications, especially Jacksonian epilepsy.[13] In a series of 39 Chinese cases Chu [24] reported one with Jacksonian epilepsy and one with hemiplegia. In American patients who contracted the disease on Leyte, P. I., Thomas and Gage [25] reported two with neurological lesions. Three others were demonstrated to the writer by Dr. James Bordley, 3rd, at the time he was Commanding Officer of the 118th General Hospital on Leyte. One of these had weakness of the muscles of the left arm, with positive Hoffmann reflex, and transient weakness of the muscles of the left leg and left side of the face. A second patient had flaccid paralysis of the left arm, with positive Hoffmann reflex, right ankle clonus and exaggerated reflexes of the right leg. The third patient, who first developed neurological symptoms six and one-half months after exposure, manifested marked weakness of the muscles of the left side of the body, numbness of the left side of the upper lip and of the left third, fourth and fifth fingers. From time to time, particularly after slight exertion or mild excitement, he exhibited Jacksonian seizures of short duration.

Several additional clinical cases of neurological complications of schistosomiasis have been seen in American Army hospitals both overseas and in the United States. Reports on one of these patients and a diagnosis made post mortem by the writer on another case will be briefly presented.

Clinical Case. (Clinical data and specimen furnished through courtesy of Major I. Joshua Spiegel.) On March 27, 1945, approximately four and a half months after arrival on Leyte, a coast artilleryman, without previous illness, developed a convulsive seizure. The next day there was a second attack preceded by an olfactory aura. From that time he exhibited classical symptoms and signs of a tumor in the right temporo-parietal area, with markedly unilateral choked optic disc. Spinal fluid revealed no abnormalities and repeated stool examinations were negative for parasite objects. He was shortly thereafter evacuated to a General Hospital in the United States. On May 23, 1945 he was operated on and a granulomatous mass about the size of an apple was removed from under the right temporo-parietal bone. Following the operation the patient made an uneventful recovery and there was marked improvement in his left hemiparesis. Section of the tumor mass revealed numerous pseudotubercles around infiltrated eggs of *Schistosoma japonicum,* which the writer was able to confirm on consultation (figure 7). Schistosomiasis had not been suspected until the microscopic slide was examined.

Autopsy Case. (Data and specimen furnished through courtesy of Dr. W. L. McNamara, Elmhurst Community Hospital, Elmhurst, Illinois.) The subject had been in New Guinea and the Philippines for two and one-half years and was discharged on October 20, 1945. He had dengue and benign tertian malaria while overseas, but had not suffered from dysentery. Shortly after his discharge he complained of dull frontal and occipital headache and dizziness, for which he did not seek medical care. He continued to work until five days before his death. On November 25, 1945 he suddenly became comatose. The family physician was called and made a tentative diagnosis of cerebral malaria. The patient died a few hours

later. Autopsy of the brain alone was permitted. A granulomatous mass about 5 cm. in diameter was found in the lateral portion of the cerebellum, which was described as "pearly gray with numerous small foci of softening. It was unencapsulated but the overlying pia mater was thick and nodular." Sections of the lesion were sent for diagnosis to the writer, who found numerous eggs of *S. japonicum* within pseudotubercles (figure 10).

In addition to the neurological lesions which have developed in American troops, at least one had cutaneous lesions, first in the abdominal skin and later in the intercostal spaces.[26] Biopsy of these lesions revealed typical viable eggs of *S. japonicum* (figure 6). Similar ectopic locations of the eggs have been reported recently from four British soldiers in Nigeria who had acquired *S. haematobium* and *S. mansoni* infection.[27]

Comment and Summary

As a result of exposure of American troops on Leyte, P. I., opportunity has been provided for the first time to carry out clinical investigation on a considerable number of patients during the early stages of schistosomiasis japonica. These studies have confirmed and materially enhanced the relatively isolated observations on these stages of the disease previously made by investigators in China and elsewhere. The symptoms, signs and physical findings have been somewhat easier to interpret in American military patients than in infected natives, because the disease was contracted within the limits of a few months as contrasted with repeated exposure over a period of years in native patients. Under these relatively ideal conditions for clinical investigation the manifestations have been found to vary qualitatively and quantitatively in different patients, owing to the amount of infection, the reaction of the patient and possibly other, unknown determinants.

There are few clinical landmarks which are in themselves definitely suggestive of schistosomiasis during the prodromal and acute stages, so that diagnosis is relatively hazardous unless there is a definite history of bathing, swimming or otherwise utilizing raw fresh water in a known endemic focus of the disease. The demonstration of the eggs of the parasite constitutes the only known method of specific diagnosis. This requires experience, skill and at times repeated examinations on the part of the laboratory worker. Inexperience has been responsible for incorrect diagnosis and has subjected persons to unnecessary treatment and the anxiety attendant on the belief that the disease had been contracted. Likewise, inexperience has undoubtedly been responsible for failure to find eggs of the parasite when they were probably present in scant numbers in the stools of individuals complaining of vague abdominal symptoms.

Physicians who have been in charge of patients suffering from schistosomiasis are not likely to forget their experience. Those who have not had this opportunity should consider the possibility of this disease in veterans who were on Leyte or elsewhere in endemic foci in the Orient and have returned to civilian life.

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AMEBIASIS OF THE LIVER: CLASSIFICATION, DIAGNOSIS AND TREATMENT *

By GERALD KLATSKIN,† M.D., *New Haven, Connecticut*

INTRODUCTION

AMEBIASIS of the liver is a disease of considerable interest and importance. Its protean clinical manifestations make it a difficult diagnostic problem at times, but early treatment has such an important bearing on prognosis that its prompt recognition is important. Unfortunately, most reports have emphasized the clinical picture of amebic abscess, usually a late manifestation of the disease, so that many cases go unrecognized and untreated.

Numerous studies [1] have established the fact that amebiasis of the colon is a relatively common disease in the United States. The incidence is even higher in tropical and subtropical areas, where sanitation is notoriously bad. Surveys among American troops serving in India have revealed infection rates between 20 and 40 per cent.[2] Obviously, amebiasis is going to be an increasingly important problem when troops serving in heavily infected areas return to this country.

The incidence of liver involvement in amebiasis is not known precisely, but there is good evidence to indicate that it is considerably higher than is generally recognized. Autopsy studies have invariably demonstrated a higher incidence than clinical studies. In a large series of amebic dysentery cases collected from the literature [1] the liver was affected in 36.6 per cent of the autopsied cases and in only 4.86 per cent of the clinical cases. In Payne's[3] recent report the liver was involved in 56.7 per cent of 1000 clinical cases of amebic dysentery.

Recent studies have emphasized the early lesions of amebic infection of the liver. Palmer [4] was able to demonstrate these in 18 out of 19 cases of amebic dysentery coming to autopsy. The marked disparity between the number of cases diagnosed clinically and the number found at autopsy would seem to indicate that clinicians are not sufficiently familiar with the manifestations of this disease. This is especially true with regard to the early phases of the disease about which comparatively little has been written.

Surgical drainage was, for a long time, the treatment of choice in amebic liver abscess, but it was always attended by a disastrously high mortality rate. By the introduction of emetine therapy and, later, closed aspiration, Rogers was able to reduce the rate to very low levels.[5, 6] Today the combined use of emetine and aspiration is the most widely accepted form of treatment.[1, 7] Rogers found emetine alone very effective in the pre-sup-

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From the Department of Internal Medicine, Yale University School of Medicine.
† Formerly Chief of Medical Service, Schick General Hospital, Clinton, Iowa.

purative stage of amebic hepatitis, but felt that aspiration was usually indicated where a frank abscess had developed.[8] In a few instances, however, emetine alone has proved effective in such cases.[3, 7, 9]

The following report summarizes personal observations made in 69 cases of amebiasis of the liver studied in two United States Army hospitals in Bengal, India, from May 1943 to February 1945. During that period there were 14,688 admissions and of these 748 were discharged with the diagnosis of amebiasis. The liver was involved in 9.2 per cent of the latter. The records of seven patients transferred to the United States were not available so that the clinical data are based on 62 cases. The results of treatment, however, are known in all 69 cases and have been analyzed.

The purpose of this paper is to present a classification of amebiasis of the liver, based on a detailed analysis of its clinical manifestations and the known facts about its pathology, in the hope that it may simplify diagnosis, and to demonstrate the effectiveness of emetine therapy without aspiration.

Classification

Soon after our first encounters with amebiasis of the liver in India, it became apparent that many of our cases failed to fit the usual clinical picture of amebic liver abscess described in standard texts. A perusal of the scanty literature available to us revealed that types of liver amebiasis other than abscess had been described, but that very little emphasis had been placed on the diagnostic and therapeutic implications of their differentiation.

A consideration of its pathogenesis corroborates the view that there are several distinct types of liver amebiasis. In the evolution of the well described abscess, the liver goes through a number of stages which, when they proceed slowly enough, may be differentiated clinically. The destructive effects of *Entameba histolytica,* leading to abscess formation, are accompanied by reparative processes, so that the disease may progress at varying speeds, may halt at any stage or may even regress. The balance struck between these two opposing forces will depend on host immunity, the number, distribution, and virulence of the parasites and possibly on the effects of alcohol, trauma and bacterial infection.[1]

Entamebae histolytica reach the liver by way of the portal vein from a focus of infection in the bowel wall.[1, 10] There they lodge in the smaller radicles of the portal system. By their lytic action the amebae break through the walls of the veins and invade the connective tissue of the portal triads and then the parenchyma, where they produce small areas of liquefaction necrosis bordered by a thin meshwork of fibrinous strands and minimal round cell infiltration. The destructive process extends concentrically by invasion of amebae along open veins, by the coalescence of multiple small lesions and by infarction due to thrombosis of contiguous intrahepatic portal veins. This leads ultimately to the formation of the typical single amebic abscess. When amebae reach the liver in large numbers and are widespread, multiple abscesses may be produced. Grossly, early liver abscesses may be quite small

and solid. Later, they become gelatinous and finally are filled with characteristic reddish-brown fluid which contains little if any cellular exudate. The acute abscess has no capsule and may extend so rapidly it ruptures into neighboring structures. In the more slowly developing abscess a thick fibrous capsule is produced which limits further extension.

Rogers [11] points out that most of the amebae reaching the liver become engulfed in thrombosed interlobular veins and undergo degeneration before they can escape the vessel walls. The process gives rise to a congestion of the liver which can be detected clinically and to which Rogers has given the name pre-suppurative amebic hepatitis.

In a study of 19 cases of amebic dysentery coming to autopsy, Palmer [4] found a patchy increase of portal connective tissue in 18. These findings were associated to a variable extent with proliferation of the bile ducts, lymphocytic and monocytic infiltration of the portal areas, mid-zonal fatty degeneration and increased pigment in parenchymal and Kupffer cells. He believes this patchy fibrosis represents the healed stage of multiple small amebic abscesses.

The concept of a pre-suppurative stage of amebic hepatitis was not entirely new when Rogers introduced it, as Chevers and Maclean [12] had used ipecacuanha in tropical hepatitis to prevent abscess formation as early as 1886, even before the etiology of the disease was known. Rogers, however, was the first to describe it accurately, and to demonstrate the efficacy of emetine therapy. Later he pointed out that pre-suppurative hepatitis occurs in acute and chronic forms. He found it impossible to differentiate the acute form from multiple small amebic abscesses clinically, but felt it was of no importance since both responded equally well to emetine therapy.[8]

Both clinical and autopsy studies have established acute and chronic forms of amebic liver abscess. Berne [7] has pointed out that, although textbooks and literature from the Orient stress the chronic form, 58 per cent of the cases he found in Southern California were acute. Of the frank abscesses reported in the present study, all were of the acute type. There is reason to believe that the great preponderance of the chronic form in the Orient is related to the inadequacy of medical facilities there and to the failure of patients to report symptoms early.

In analyzing the 62 cases presented in this report it was found they fell into four distinct groups which were readily differentiated clinically:

Acute amebic liver abscess	7 cases
Acute amebic hepatitis	16 cases
Subacute amebic hepatitis	32 cases
Chronic amebic hepatitis	7 cases

There were no cases of chronic amebic abscess. The acute, subacute and chronic amebic hepatitis cases fell into the corresponding groups of pre-suppurative hepatitis described by Rogers, but it was deemed advisable to drop the term "pre-suppurative" since one could not say with certainty that miliary abscesses or even larger central abscesses did not exist, especially in

the acute hepatitis group. Rogers [8] suggests that leukocytosis which does not decline appreciably or disappear after one week of emetine therapy indicates the presence of an abscess. This point of differentiation was found to be unreliable in our experience. Leukocytosis subsided in less than a week in several cases of frank abscess, and persisted for longer than a week in many cases of very mild subacute amebic hepatitis.

The acute abscess cases were characterized by liver pain, high fever and frequently by cough. A definite mass was demonstrable in the liver either by palpation or by roentgen examination in every instance. The right lobe of the liver was generally enlarged and exhibited compression tenderness. Abnormal pulmonary findings were frequent. Marked leukocytosis with only slight increase in the percentage of polymorphonuclears was the rule.

The acute hepatitis cases resembled the abscess cases except that no mass could be demonstrated in the liver, liver pain and cough were less common, diarrhea and cramps were more common and leukocytosis was less marked.

The subacute hepatitis cases differed markedly from the others. Only half of them complained of liver pain. Many were admitted because of diarrhea and cramps and were found to have enlarged tender livers. Fever was inconstant and when present was low grade in character and intermittent. Cough and abnormal pulmonary findings were unusual. Leukocytosis occurred infrequently and when present was usually mild.

In contrast to the first three groups of cases, in which symptoms were usually present for less than 10 days, the chronic hepatitis cases were admitted with liver pain of long duration, ranging from two to 12 months. As in the case of subacute hepatitis, fever and leukocytosis were inconstant. Diarrhea was fairly common and cough and abnormal pulmonary findings occurred occasionally.

Although it must be admitted that the classification outlined is open to question since small centrally placed abscesses could not be excluded in the hepatitis groups, the detailed analysis of the data will demonstrate clear-cut clinical differences between them. It must be remembered that cases in one group may advance or regress to another, either as a result of treatment or spontaneously under the influence of factors already discussed.

Classifying these cases makes for a better understanding of the underlying pathology, calls attention to the less commonly recognized forms of the disease and gives some indication of the amount and type of treatment required.

The following case histories will illustrate each of the groups mentioned:

Case Reports

Case 1. Acute Amebic Abscess of the Right Lobe of the Liver (Figure 1).

History. A 47-year old officer was admitted to the hospital on September 4, 1943, complaining of abdominal cramps. Four days before admission there was a sudden onset of generalized abdominal cramps, nausea, and watery diarrhea. He was given bismuth and paregoric with prompt relief. Two days later he developed epigastric

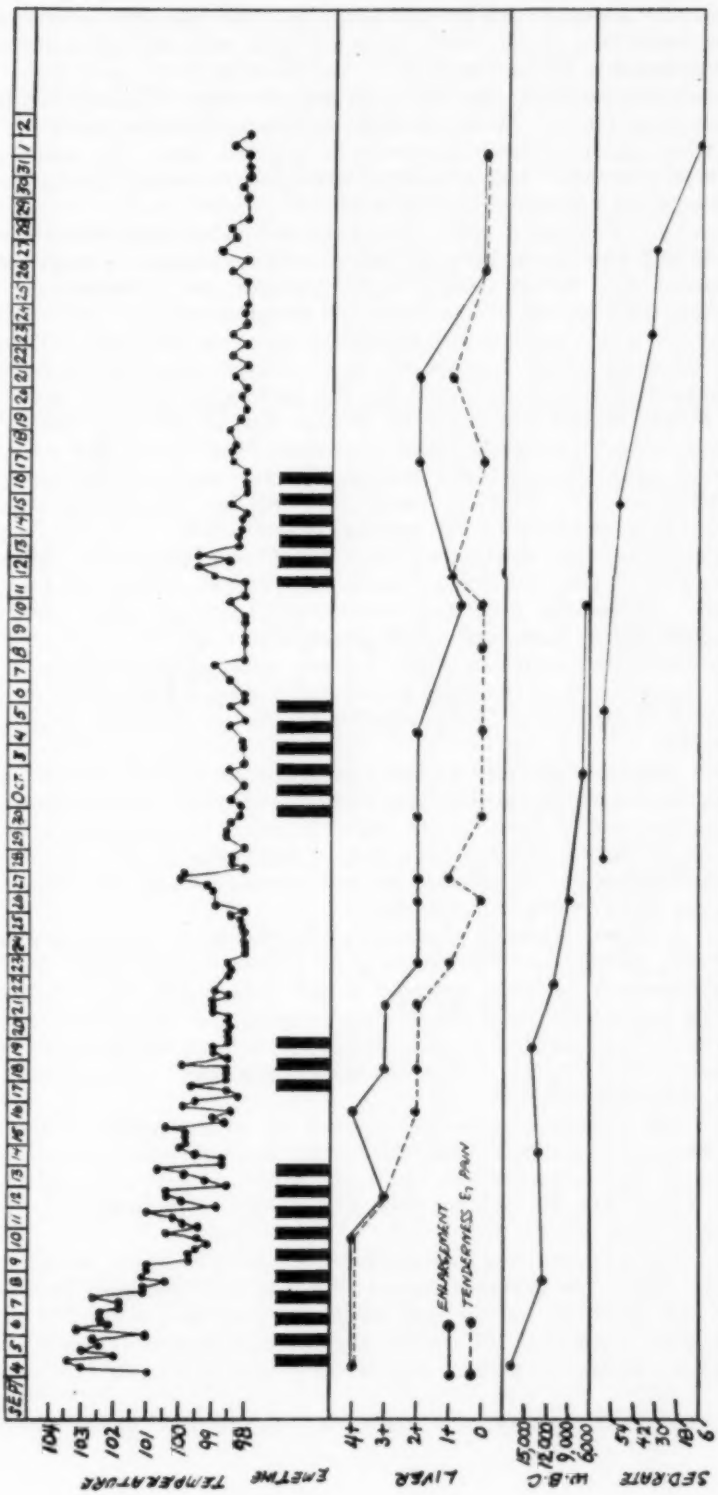

FIG. 1. *Case 1.* Acute amebic abscess of the right lobe of the liver.

pain, fever, chilly sensations and profuse sweating. The epigastric pain was crampy in character, moderately severe, radiated to the back, and was aggravated by deep breathing, movement in bed and by lying on the left side.

The patient had spent six weeks in China and six weeks in India just prior to the onset of his present illness. Shortly after his arrival in China he had had a mild attack of diarrhea which subsided spontaneously in a few days. He denied previous gastrointestinal symptoms. Alcoholic consumption was moderate. He had lost seven pounds in weight since his arrival in the Orient.

Examination. The patient was a well nourished middle-aged man who appeared moderately ill and who lay on his right side to relieve his pain. Complexion sallow and conjunctivae pale, but no definite icterus demonstrable. Temperature 101° F., pulse 80, respirations 20. Eyes, ears, nose and throat normal. Trachea in mid-line. Thyroid normal. Chest symmetrical, expansion equal on both sides. Compression of right lower chest caused considerable pain. Lungs clear. Heart normal. No signs of elevated diaphragm by percussion, but both bases descended poorly on inspiration. Blood pressure 125 mm. Hg systolic and 65 mm. diastolic. Abdomen soft, flat, symmetrical. Moderately firm, exquisitely tender liver edge palpated four fingers'-breadth below the right costal margin. Anterior surface of the liver definitely convex. Spleen not felt. Genitalia normal. No hernia. Extremities normal. No ankle edema. Reflexes in order. No enlarged lymph nodes.

Laboratory Findings. Red blood cells 4,750,000. Hemoglobin 90 per cent. White blood cells 16,150. Differential smear: polymorphonuclears 86 per cent (11 stabs, 75 segs.), eosinophiles 1 per cent, lymphocytes 11 per cent, monocytes 2 per cent. Urinalysis: dark amber, hazy, acid specific gravity 1.024, albumin 2 plus, sugar negative. Microscopic: few epithelial cells. Routine stool: precystic forms of *E. histolytica.* A second specimen examined on September 30 revealed actively motile vegetative forms of *E. histolytica.* Kahn negative. Sedimentation rate: 58 mm. in one hour (Wintrobe).

Roentgen Studies. September 4: chest roentgenogram negative, except for slightly elevated left diaphragm due to distended colon. Abdominal roentgenogram showed downward enlargement of liver, 4.5 cm. below the costal margin, and marked distention of the splenic flexure and descending colon. September 29: chest roentgenogram negative. Roentgenogram of abdomen showed increased downward enlargement of the liver, 6 cm. below the right costal margin.

Course. A clinical diagnosis of amebic abscess of the liver was made on admission and emetine therapy was started, one grain intramuscularly daily. For the first few days the patient's condition appeared to get worse. He ran a high remittent fever, ranging between 101° and 103.5°, the abdominal pain increased and interfered with sleep, the convexity of the anterior surface of the liver increased, giving rise to a poorly defined dome-shaped mass beneath the right upper rectus muscle, and he developed a dry irritative cough.

The first sign of improvement was a definite fall in temperature on the fifth day of emetine therapy. Liver pain and enlargement began to subside three days later. The temperature was normal by the fourteenth day, liver pain and tenderness were gone by the twenty-first day and the liver had receded to the costal margin by the fifty-first day.

The first course of treatment consisted of 10 grains of emetine. After an interval of three days, three more grains were given because fever and pain persisted. The temperature fell to normal and the pain subsided. Two more courses of emetine, 6 grains each, were required at 10- and six-day intervals because of recrudescences of fever and pain. In all, the patient received 25 grains of emetine over a period of 43 days.

Concomitant with the last two courses of emetine the patient received both

carbarsone and chiniofon. Check stools at the end of treatment were negative for *E. histolytica.*

The white blood count gradually fell as the liver receded and was normal by the twenty-second day. The sedimentation rate, however, remained elevated long after hepatic tenderness was no longer demonstrable and did not reach normal until the fifty-ninth day.

During the first three weeks of his illness, the patient lost considerable weight. His appetite returned to normal when he was afebrile and his weight gradually returned to its previous level.

On discharge from the hospital on the sixtieth day, the patient felt perfectly well and he was returned to full military duty. His liver edge was still palpable at the costal margin, but it was no longer tender and there was no compression tenderness of the right lower chest.

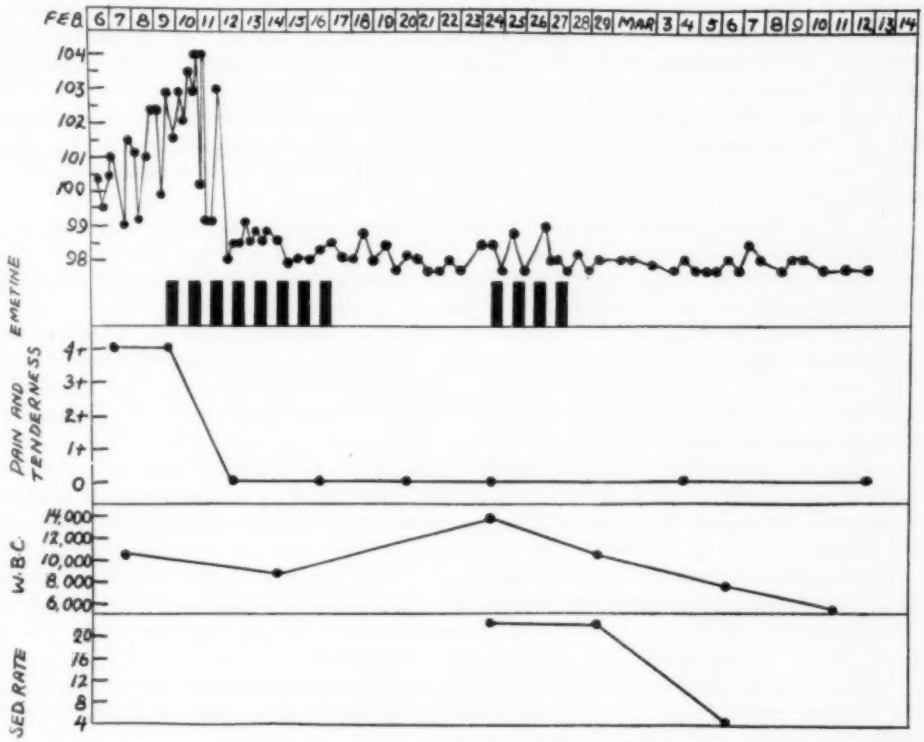

FIG. 2. *Case 2.* Acute amebic hepatitis.

Case 2. Acute Amebic Hepatitis (*Figure 2*).

History. A 27-year old colored soldier was admitted to the hospital on February 6, 1943, with the history of a sudden onset of severe sharp pain in the right lumbar region, right shoulder and right side of the neck two days before admission. The next day he had developed a head cold and cough productive of a small amount of mucus.

The patient had been in India for 21 months. Four months after his arrival, he had contracted amebic dysentery for which he had received what is said to have been adequate treatment. Since then he had had no gastrointestinal symptoms. He drank very little alcohol. His past history was otherwise non-contributory.

Examination. The patient was well developed and well nourished and did not appear ill. Temperature 100, pulse 84, respirations 21. Nasal and pharyngeal mucosa inflamed. Slight splinting of right side of chest with suppression of the breath sounds at the right base. No impairment of resonance or râles. No friction rub heard. Heart normal. Abdomen normal except for tenderness on deep palpation beneath the right costal margin. Liver not felt.

Laboratory Findings. White blood cells 10,330. Differential count: polymorphonuclears 74 per cent, lymphocytes 26 per cent. Urinalysis: amber, clear, acid, specific gravity 1.021, albumin negative, sugar negative; microscopic: occasional mucous threads and calcium oxalate crystals. Kahn reaction doubtful on first test, negative on second test. Sedimentation rate: 22 mm. in one hour. Two routine stools negative for *E. histolytica.*

Roentgenographic Studies. Chest negative.

Course. The admission diagnosis was: (1) Nasopharyngitis, (2) pleurisy or amebic abscess of the liver. The temperature gradually rose in step-like fashion reaching a maximum of 104° on the fourth day. The pulse rate was proportionally increased and the respiratory rate ran between 24 and 26. There were several shaking chills.

The day after admission the patient localized his pain in the right lower chest and anterior-posterior compression was found to cause considerable pain. It continued to radiate to the right shoulder and the right side of the neck, especially on deep inspiration. At no time could the liver be felt.

In view of the negative chest film, the high fever, the leukocytosis, the compression tenderness of the right lower chest and the history of amebic dysentery in the past, a diagnosis of acute amebic hepatitis was made and emetine therapy started, one grain daily.

There was a marked drop in temperature and the pain and compression tenderness disappeared after the third dose of emetine. The temperature reached normal and remained so after five grains of emetine. The white blood cell count and the sedimentation rate remained elevated for some time and returned to normal 28 days after emetine had been started.

The first course of emetine consisted of 8 grains. After an interval of seven days, a second course of 4 grains was given. The latter was supplemented with a course of chiniofon. A check stool at the end of treatment was negative for *E. histolytica.*

The patient was discharged on the thirty-sixth day at which time he felt perfectly well. Abdominal and chest examination was entirely normal and he was returned to full duty.

Case 3. Subacute Amebic Hepatitis.

History. A 25-year old officer with 13 months' service in India, was admitted to the hospital on October 30, 1944 complaining of intermittent watery diarrhea, and abdominal pain.

Ever since his arrival in India the patient had had frequent attacks of watery diarrhea lasting two to three days. These had subsided spontaneously or following the administration of sulfaguanidine. In February 1944, a single stool specimen had been examined and found to be free of *E. histolytica.* His last attack of diarrhea had started three days before admission.

For the two weeks preceding admission, the patient had been troubled with abdominal pain. At first the pain had been located in the lower abdomen and had been aggravated by physical exercise and relieved by defecation. Later, it had shifted to the right upper quadrant beneath the costal margin and was described as sharp and intermittent. It did not radiate and was unaffected by deep breathing, lying on the side, twisting, bending or jarring.

There had been no fever, chills or other constitutional symptoms. Past history was non-contributory.

Examination. The patient lay in bed without apparent discomfort and did not appear ill. Skin normal, no icterus. Eyes, ears, nose, throat normal. Lungs clear on auscultation and percussion. Heart normal. Moderate anterior-posterior and mild lateral compression tenderness of the right lower chest. Abdomen soft with tenderness beneath the right costal margin, and to a lesser degree in the left lower quadrant and peri-umbilical region. On the first examination the liver could not be felt. Two days later it was easily palpable two fingers'-breadth below the costal margin and was found to be soft and moderately tender. Remainder of examination normal.

Laboratory Findings. White blood cells 5,500. Differential smear: polymorphonuclears 79 per cent, lymphocytes 14 per cent, monocytes 6 per cent, eosinophiles 1 per cent. Sedimentation rate: 14 mm. in one hour. Stool positive for *E. histolytica.*

Course. Emetine therapy, one grain daily, was started as soon as *E. histolytica* was demonstrated. Liver pain and tenderness began to subside on the third day and were absent on the fourteenth day of treatment. The liver edge receded rapidly, but was still palpable at the costal margin on the fifteenth day when the patient was discharged to duty. However, it was no longer tender and there was no compression tenderness over the lower right chest. The sedimentation rate was normal on the fourteenth day.

The patient received a total of 12 grains of emetine over a 15-day period. He was also given a seven-day course of Diodoquin 0.63 gm. t.i.d., followed by a seven-day course of carbarsone, 0.25 gm. t.i.d. At the end of this treatment, three stools were examined following the administration of a large dose of magnesium sulfate and no *E. histolytica* could be demonstrated. There was no diarrhea or pain and the patient felt perfectly well.

He was discharged to full military duty on the fifteenth hospital day.

Case 4. Chronic Amebic Hepatitis.

History. A 37-year old soldier with 20 months' service in India was admitted to the hospital on November 30, 1944 complaining of pain in his upper abdomen.

For one year he had experienced pain in the right upper quadrant. The pain was sharp in character, moderately severe and was brought on by jarring, such as occurred while riding in a truck over rough roads, by deep breathing and by twisting or turning suddenly. It frequently occurred at night while he lay on his back and it was relieved by lying on either side. At times it radiated to the right lumbar region.

There was no relationship between the pain and the ingestion of food and the patient denied indigestion, diarrhea, cramps, intolerance for fatty foods and jaundice in the past. At times he had noted nausea, but never any vomiting.

There were no cardio-respiratory or genito-urinary symptoms. The past history was non-contributory.

Examination. The patient was a husky man of 37 who did not appear ill. Skin was normal, no icterus or pallor. There was moderate dental caries. Nose and throat were normal. Chest was symmetrical. Anterior-posterior and lateral compression of the right lower chest caused pain. Lungs were normal on percussion and auscultation. There was marked tenderness without spasm beneath the right costal margin. The liver by percussion was two fingers'-breadth below the costal margin, but its lower edge could not be palpated owing to a thick abdominal wall. The next day it was easily palpable one finger's-breadth below the costal margin and it was found to be moderately tender. Kidneys and spleen were not felt. Extremities were normal. Reflexes were physiological.

Laboratory Findings. Red blood cells 4,890,000. Hemoglobin 90 per cent. White blood cells 11,900. Sedimentation rate: 21 mm. in one hour. Urine: straw

color, clear, acid, specific gravity 1.017, albumin negative, sugar negative. Stool examination, after one ounce of magnesium sulfate, revealed actively motile trophozoites of *E. histolytica*.

Roentgenographic Studies. Cholecystogram after oral dye showed normal filling and emptying of the gall-bladder. No biliary calculi were demonstrated.

Course. Emetine therapy, 1 grain daily, was started the day after admission. Pain and liver tenderness were definitely diminished on the fourth and absent on the twelfth day of therapy. The liver was no longer palpable and compression tenderness of the right lower chest was absent on the sixth day. The sedimentation rate had dropped to 10 mm. in one hour by the tenth day. A total of 12 grains of emetine was given over a 15-day period. The entire course was afebrile except for rises to 99 on two occasions.

The emetine therapy was supplemented with a course of Diodoquin, 0.63 t.i.d. for seven days and a course of carbarsone, 0.25 gm. t.i.d. for seven days. Check stools, after a dose of magnesium sulfate, were negative for *E. histolytica*.

The patient was discharged on the nineteenth hospital day and returned to full military duty.

Predisposing Factors

Alcohol. The rôle of alcohol as a predisposing factor in the development of hepatic amebiasis has been a matter of controversy.[1, 7] In the present series no relationship could be demonstrated between the two. Of the 62 cases, 23 were total abstainers, 18 drank very little and 21 drank moderately.

Age. The average age was 29.8 years, considerably higher than the average for all admissions to the hospital. Thirty-three patients were between the ages of 20 and 29, 24 between 30 and 39, and five between 40 and 49. The youngest patient was 20 and the oldest 47. In general these findings confirm the consensus of opinion that the disease occurs chiefly between 30 and 50 and that it is rare below the age of 20 or above 50.[1, 7]

Sex. No sex preponderance could be demonstrated when the relative admission rates for males and females were taken into account. Two of our 62 cases were female—an incidence of 3.2 per cent which was slightly higher than the average admission rate for females. Other observers [1, 13] have noted a much greater susceptibility of males to the disease.

Race. Natives in the tropics are said to show a much lower incidence of hepatic amebiasis than Europeans.[1] This is difficult to explain since the former almost certainly have a higher colonic infection rate. A recent study by Payne [3] casts considerable doubt on the concept of racial immunity. No such immunity has been demonstrated in the negro and our findings confirm this. Six of our 62 cases were negroes—an incidence of 9.7 per cent which was a little higher than the average negro admission rate.

Trauma. In some instances trauma has precipitated the development of an amebic abscess of the liver.[7] There was no history of trauma to the liver in any of our cases.

Amebic Dysentery. Only eight of our cases (13 per cent) gave a definite history of amebic dysentery in the past, but 39 (63 per cent) had a history of intermittent diarrhea suggesting amebiasis.

The interval between the attack of dysentery and the onset of hepatic amebiasis averaged 7.3 months. The shortest interval was two weeks, the longest 17 months.

In those with a history of intermittent diarrhea it had been present on an average of 5.6 months (one week to 20 months).

Although a history of antecedent amebic dysentery is often lacking, there is good evidence to support the view that hepatic amebiasis is invariably preceded by amebic ulceration of the colon. Many of the latter are asymptomatic and some have healed by the time liver disease becomes apparent clinically. In Rogers' series of amebic abscess cases coming to autopsy, 77.8 per cent had evidence of active dysentery and 20 per cent demonstrated the scars of healed dysentery.[11]

Residence in the Tropics. The average residence in the tropics before the development of symptoms was 11.8 months. The shortest was six weeks, the longest two years. Most of the patients had served in India only, but there were a few who had also served for varying periods in China, Iran and North Africa.

Symptoms

Onset. In general, the onset of symptoms was sudden in abscess and acute hepatitis and gradual in subacute and chronic hepatitis. The duration of symptoms before admission to the hospital averaged less than 10 days in abscess, acute and subacute hepatitis, and averaged 5.7 months in chronic hepatitis (table 1).

Table I

Onset and Duration of Symptoms before Admission to the Hospital

	Onset		Duration	
	Sudden	Gradual	Average	Range
Acute abscess	5 cases	2 cases	5.4 days	3–8 days
Acute hepatitis	10	6	3.4 days	1–10 days
Subacute hepatitis	10	22	8.7 days	2–30 days
Chronic hepatitis	0	7	5.7 mos.	2–12 mos.

The initial symptoms were quite variable, but generally, in the course of a few days others developed which clearly indicated the nature of the disease. The abscess and acute hepatitis cases usually came to the hospital because of fever and liver pain, but a few had only fever, cough, chest pain or diarrhea. Onset with liver pain was much less common in subacute hepatitis, and fever was rarely an initial complaint. Many of these patients started with diarrhea and cramps and only later developed liver pain. Several were actually under treatment for amebic dysentery when symptoms of hepatic involvement appeared. All the patients with chronic hepatitis came to the hospital because of liver pain. In a few the pain had been preceded

or accompanied by diarrhea, but the latter was never the cause for admission and was usually considered insignificant.

Liver Pain. Liver pain was by far the most common symptom in all forms of hepatic amebiasis. It occurred in all the abscess and chronic hepatitis, in most of the acute and in about half of the subacute hepatitis cases (figure 3).

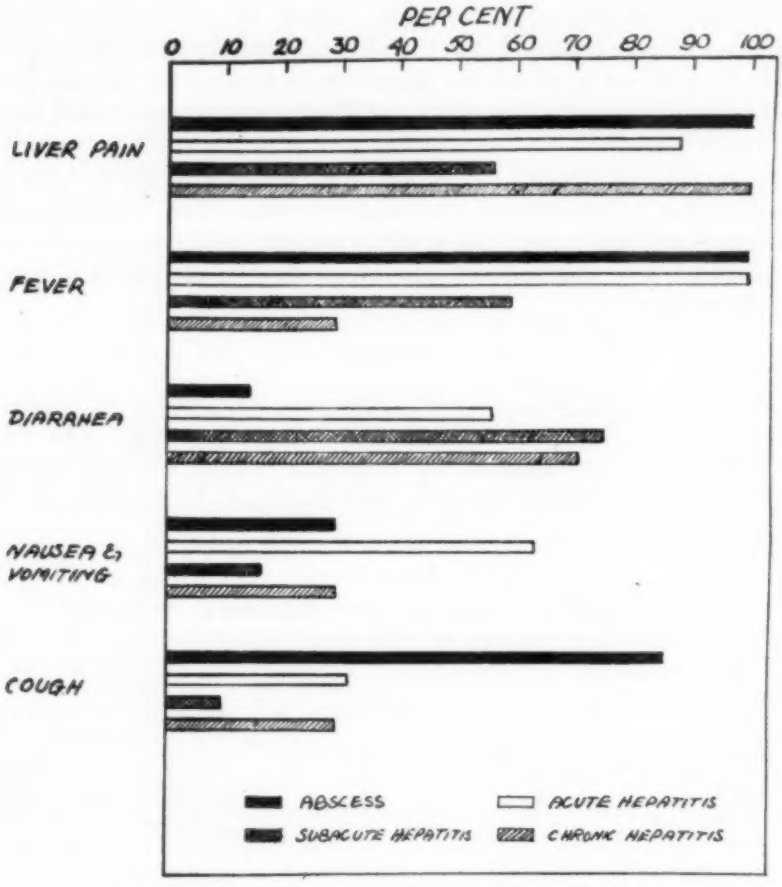

FIG. 3. Principal symptoms of hepatic amebiasis.

The pain had a number of distinctive features, which, when carefully analyzed, usually indicated the liver and excluded other structures above and below the diaphragm as the source of the pain. These features were its location, character, severity, radiation and aggravation by movements and change in position (figure 4).

Liver pain was usually localized in the right upper quadrant of the abdomen beneath the costal margin. Characteristically many of the patients indicated its location with the fingers cupped and resting just below the right

costal margin. It was localized less commonly in the epigastrium and in the right lower chest.

In three cases (one abscess, one acute hepatitis and one chronic hepatitis), the pain was localized in the left upper quadrant, and the clinical evidence indicated primary involvement of the left lobe of the liver. Although the right lobe is usually involved, a number of left sided amebic abscesses have been recorded.

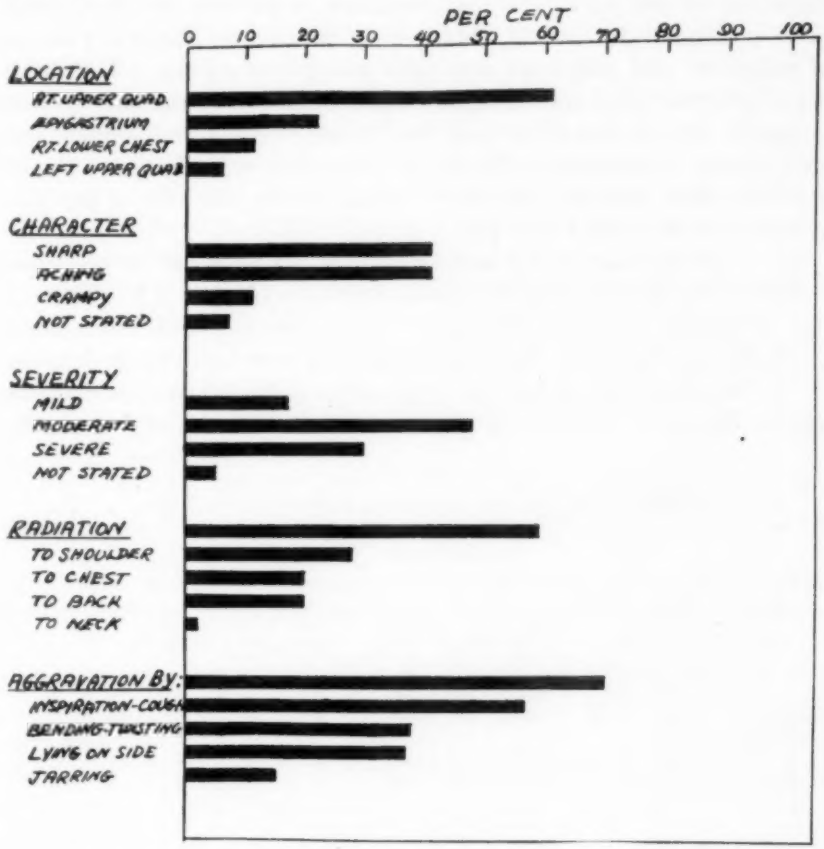

FIG. 4. Characteristics of liver pain in 46 cases of hepatic amebiasis.

As a rule it was described as a constant ache, or an intermittent sharp pain, usually brought on by characteristic movements or change in position. Although a few patients described it as crampy, it was never colicky, as in ureteral or biliary colic.

For the most part the pain was only moderate in severity. Most of the cases with severe pain fell into the abscess and acute hepatitis groups. Only three patients with subacute hepatitis had severe pain.

Aggravation of the pain by movements and change in position was a prominent feature and was of great diagnostic significance. The principal

aggravating factors were deep breathing and cough, bending and twisting, lying on either side and jarring. Frequently the patient spontaneously offered the information that these produced or aggravated his pain, but in many instances it was necessary to inquire specifically about their effect. The effect of jarring, especially on riding over rough terrain, probably occurred more frequently than indicated, as many of our patients were not asked about it.

Radiation of the pain was very common, especially on movement or change in position. In several instances the first complaint was pain at the site of radiation, and only later was pain noted in the liver. This led to a number of diagnostic errors, especially when radiation to the chest occurred. The common sites of radiation were the shoulder, chest and lumbar region. On one occasion it radiated to the neck. Radiation was always to the right, except in the three patients with involvement of the left lobe of the liver in whom radiation occurred to the left.

Fever. All the abscess and acute hepatitis, but only half of the subacute and a third of the chronic hepatitis cases had fever (figure 3). There were striking differences between the fever of the abscess and acute hepatitis groups on the one hand and the subacute and chronic hepatitis groups on the other. In the former it was always high and usually remittent or continuous, whereas in the latter it was low-grade and usually intermittent (table 2).

TABLE II

Characteristics of Fever Exhibited in Hepatic Amebiasis

	Patients	With Fever	Height of Fever		Type of Fever			Chills	Sweats	Brady-cardia
			Average Maximum	Range	Continuous	Remittent	Intermittent			
Abscess	7	7	103.4	102.5–104	1	6	0	5	4	5
Acute hepatitis	16	16	103.4	101.5–105	2	11	3	10	6	9
Subacute hepatitis	32	19	100.3	99.5–102	0	2	17	1	0	0
Chronic hepatitis	7	2	100.9	99.5–102.3	0	0	2	1	0	1

There were only two cases of subacute hepatitis with a fever over 101° and in both instances it was very irregular and intermittent. One case of chronic hepatitis, with a history of liver pain for three months, had an intermittent fever up to 102.3 for eight days. It was felt he was entering the acute phase of the disease.

Chills and, to a lesser extent, sweats were common in both the abscess and acute hepatitis groups. Relative bradycardia and high fever, with pulse rates between 70 and 80, were also seen frequently in abscess and acute hepatitis (table 2).

In several instances fever preceded the onset of liver pain and tenderness and the patients were thought to have one of the infectious diseases on ad-

mission to the hospital. The temperature-pulse curves in the three cases with continuous fever resembled those seen in typhoid fever.

Diarrhea. The absence of symptomatic dysentery in many abscesses of the liver has been noted by others,[1, 7] and Rogers [8] has suggested that this is due to the predominance of amebic ulcerations in the cecum and ascending colon. Diarrhea occurred but once in our abscess group, but was very common in the other groups (figure 3).

None of the cases with diarrhea had gross blood or mucus in the stools. As a rule the diarrhea was mild and the stools were mushy or watery.

Abdominal cramps, chiefly in the lower quadrant but occasionally generalized, accompanied the diarrhea in only one-third of the cases and occurred almost exclusively in the subacute hepatitis group. This was the group, it will be recalled, in which diarrhea was a frequent primary complaint. In two instances abdominal cramps occurred without diarrhea. There was rarely any difficulty in differentiating liver pain from cramps due to associated dysentery.

Nausea and Vomiting. Either or both occurred in about a third of the cases and were most common in the acute hepatitis group (figure 3).

The nausea and vomiting promptly subsided with the institution of emetine therapy and were rarely associated with anything but transient anorexia or indigestion, two points of considerable importance in differentiating this disease from infectious hepatitis.

Cough. Cough was an important symptom, especially in the abscess group although it also occurred to a lesser extent in the other groups (figure 3).

Of the 16 patients with cough, seven had chest pain. There were also nine cases of chest pain without cough. The pain in both instances was undoubtedly hepatic in origin. Nevertheless, it focused attention on the lungs, as did the cough, and led to diagnostic errors. Chest pain was the initial symptom in eight cases and was associated with cough in seven and fever in five.

As a rule the cough was dry and irritative, but in one-third of the cases it was productive of sputum.

Physical Findings

General Appearance. The patients with abscess and acute hepatitis usually appeared acutely or moderately ill, while those with subacute and chronic hepatitis appeared mildly ill or not ill at all (table 3).

A few patients showed evidence of recent *weight loss,* but it was never marked. It is apparently a much more frequent finding in chronic amebic abscess.

The *sallow complexion* said to be characteristic of hepatic amebiasis was seen in only five patients—one acute abscess, three acute hepatitis and one chronic hepatitis. It too probably occurs principally in the chronic abscess group.[1]

TABLE III
Apparent Severity of Illness on Examination

	Acute	Moderate	Mild	Not Ill
Abscess	3	2	1	1
Acute hepatitis	6	3	2	5
Subacute hepatitis	0	2	0	28
Chronic hepatitis	0	0	1	6

Clinical *jaundice* was not seen in any of our patients, although the icteric index was 19 in one and traces of bile were found in the urines of five. Frank jaundice has been reported in 10 to 30 per cent of patients with hepatic amebiasis,[1, 13] but Brown and Hodgson [13] report that it is never intense. It would appear from the cases reported that jaundice also occurs chiefly in the chronic abscess group.

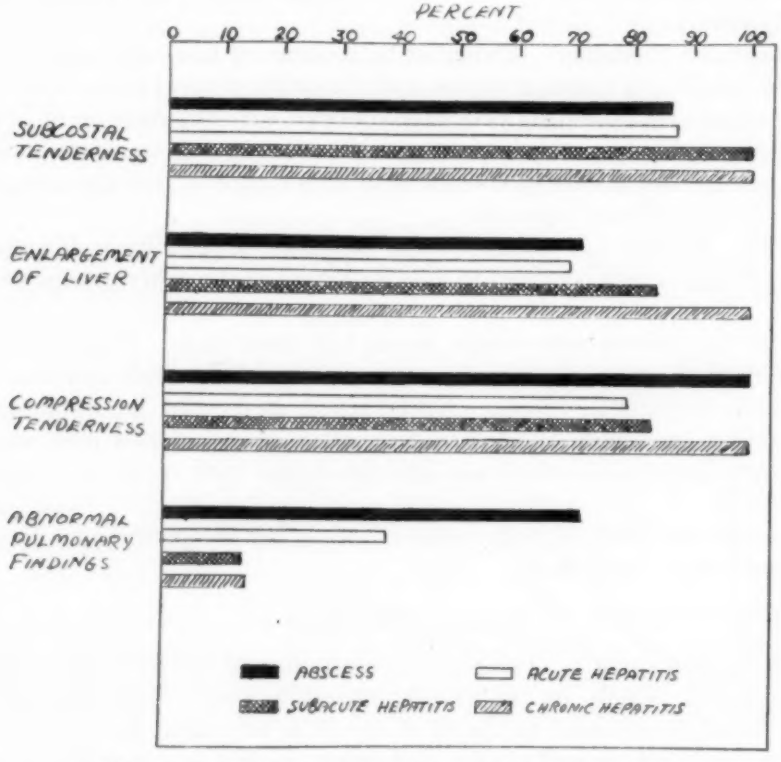

FIG. 5. Principal physical findings in hepatic amebiasis.

Abdominal Findings. *Subcostal tenderness* was the most frequent abnormality noted (figure 5). It occurred in all the subacute and chronic hepatitis and in most of the other cases. It was associated with spasm of the upper right rectus muscle in eight patients.

Palpable enlargement of the liver was easily demonstrable in most of the patients, but it was absent in two with abscess, five with acute hepatitis and five with subacute hepatitis (figure 5). The enlargement varied from one to four fingers'-breadth below the right costal margin. In two of the three cases with left lobe involvement, the right lobe was also enlarged. The liver edge was usually soft and sharp and was always tender. Tenderness varied considerably from case to case, but was, in general, most severe in abscess and acute hepatitis. Subcostal tenderness frequently preceded palpable enlargement by several days.

A definite visible and palpable bulge of the liver was demonstrable in six of the seven abscess cases. In the seventh it was demonstrable by roentgen-ray only. It was located in the epigastrium in three, beneath the right lower ribs in two and beneath the left costal margin in one. The swelling was usually doughy and invariably exquisitely tender. Fluctuation was never demonstrated. The overlying skin showed no changes, but in one case, involving the left lobe, the overlying abdominal wall seemed edematous and tender and attached to the underlying mass.

Upward enlargement of the liver was demonstrated by percussion in three and by roentgen-ray in eight cases.

Compression tenderness of the liver was a finding of considerable importance and was present in 43 of the 50 cases tested. It was demonstrated in all the abscess and chronic hepatitis and in most of the acute and subacute hepatitis cases tested (figure 5). Tenderness was elicited by compressing the lower right chest anterior-posteriorly between the palms of the hands. The test was considered positive only when the patient complained of moderate to severe pain. As a rule subjective pain was associated with wincing. Mild pain or a feeling of pressure was not considered significant. Except when anterior-posterior tenderness was severe, lateral compression tenderness was usually not demonstrated. In the three cases of left lobe involvement, compression tenderness was demonstrated on the left, and in one, it was present on both sides.

The compression test proved to be of great help in differential diagnosis. It clearly demonstrated the hepatic origin of the pain and differentiated it from that arising in other structures above and below the diaphragm. The test was tried in a great variety of conditions including pneumonia, pleurisy, renal colic, pyelitis, acute dysentery, peptic ulcer and malaria with enlargement of the liver and was invariably negative. It was also of some value in differentiating amebic from infectious hepatitis. In a large series of infectious hepatitis cases, in which the test was tried, it was negative in all but a few. The only other condition in which the test was invariably positive was acute cholecystitis. No doubt there are other conditions, such as subphrenic abscess, in which the test may be positive.

Compression tenderness is by no means to be considered pathognomonic of hepatic amebiasis, but it has proved its worth as a confirmatory finding, and in a few instances it has made an early diagnosis possible in the absence

of other findings. In five cases, one abscess, two acute hepatitis and two subacute hepatitis, it was the only physical finding other than fever on admission to the hospital. Subsequently in three of them liver enlargement and subcostal tenderness became apparent. The compression test has been found valuable by others,[13] but it has never received the emphasis it deserves.

Of the 62 cases, 61 showed one or more of the three principal physical findings—compression tenderness, subcostal tenderness and palpable liver enlargement (table 4). The last case came to the hospital with severe right

TABLE IV

Principal Abdominal Findings

	Early*	Late
Compression tenderness alone†	5	2
Subcostal tenderness alone	1	0
Liver enlargement alone	0	0
Combination of any two signs	29	26
Combination of all three signs	25	33
No signs	2	1

* On admission to the hospital. † Tested in 50 cases.

subcostal pain, aggravated by breathing, movement and lying on the left side, and a remittent fever up to 104°. Physical examination was entirely negative except for a few râles at the left base. The white blood cell count was 13,650 with 69 per cent polymorphonuclears. A routine stool was negative for *E. histolytica,* and a roentgen-ray of the chest was normal. On emetine therapy there was a prompt clinical response, with subsidence of pain, fever and leukocytosis.

Percussion tenderness over the liver has been stressed by some,[14] and it was found to be present in a few of the cases in which it was tested.

Only one of our patients had a localized area of tenderness in the intercostal spaces, a sign said to be of some merit in the diagnosis of amebic abscess.

Many of the patients with associated dysentery had mild tenderness along the course of the colon, especially in the right lower quadrant. The cecum was occasionally thickened and tender.

The spleen was palpable in only one patient. Since he had lived in a malarious area for some time, it was considered unrelated to the liver disease.

Pulmonary Findings. Abnormal physical findings were noted in the chest in 26 per cent of our patients. They were common in the abscess group, but also occurred to a lesser extent in the others (figure 5). The abnormalities were always in the right lower lobe, except in the three cases of left sided hepatic amebiasis.

The physical signs were definite, although never marked, and usually suggested early pneumonia (table 5).

ROENTGEN-RAY FINDINGS

Chest. Roentgen-ray examination of the chest was performed in 36 patients and abnormalities were noted in 17. As in the case of cough and

TABLE V

Abnormal Pulmonary Physical Findings Found in 16 Patients with Hepatic Amebiasis

Increased respiratory rate (over 25 per min.)	16
Suppressed breath sounds	11
Dullness on percussion	5
Râles	5
Splinting of the lower chest	5

abnormal chest findings on physical examination, they were most common in the abscess and acute hepatitis groups (table 6).

TABLE VI

Chest Roentgen-Ray Findings in Hepatic Amebiasis

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis	Total
Number of patients examined	7	12	13	4	36
Number with abnormal findings	5	7	4	1	17
Diaphragm					
Elevation	3	4	1	0	8
Flattening	2	0	1	0	3
Obliteration of C.H.†	0	1	0	1	2
Limited motion*	0	1	0	0	1
Local bulge	1	0	0	0	1
Lungs					
Increased markings	2	5	3	1	11
Haziness	1	0	0	0	1
Effusion (slight)	0	0	1	0	1

* Number of fluoroscopic examinations not known.
† C.H. = cardiohepatic angle.

When abnormalities were noted in the lungs they were usually interpreted as probable early pneumonia, and the roentgenologist frequently recommended a second roentgen examination in 24 to 48 hours. This was especially true when the clinical history was not submitted with the request for roentgen-ray examination. When the clinical diagnosis of hepatic amebiasis was suggested or when the diaphragm was elevated, the roentgenologist frequently confirmed the diagnosis. In brief then, the findings in most cases were not sufficiently characteristic to warrant a diagnosis of hepatic amebiasis. Unfortunately fluoroscopy was not done routinely so that the question of diaphragmatic movement was not investigated in every case.

Of the 15 patients with involvement of the right lobe of the liver who exhibited abnormalities in the chest roentgen-ray, 14 had them at the right base and in the right leaf of the diaphragm, and one had lung changes at both bases. Of the two patients with involvement of the left lobe of the liver with roentgenographic abnormalities, one had them on the left, the other bilaterally.

It seemed probable to us that the pulmonary changes found were due to a mild degree of atelectasis, secondary to splinting of the chest, to pressure of the liver from below and to partial or total restriction of the right hemidiaphragm. The elevation and immobility of the diaphragm are thought to

be due to inflammation and edema by direct extension from the underlying inflamed liver.[15] It is not surprising, therefore, to find so few changes in the diaphragm in the present report, since most of the cases were seen very early and since in only one of the cases was it possible to demonstrate an abscess in the dome of the liver. Munk [15] has stressed the fact that signs in the diaphragm are lacking where the enlargement of the liver is chiefly anterior and inferior.

In more advanced cases, and particularly with abscesses located close to the dome of the liver, one frequently finds pleurisy, pleural effusion and true pneumonitis.[7, 16] These cases also usually exhibit roentgen findings which are considered diagnostic of liver abscess—namely, elevation, fixation and local bulging of the diaphragm, obliteration of the cardiohepatic angle in the postero-anterior view and obliteration of the anterior costophrenic angle in the lateral view. Subphrenic abscess due to other causes, on the other hand, gives a similar picture, but the costophrenic angle is obliterated laterally in the postero-anterior view and posteriorly in the lateral view.[1]

Only one of our cases had a mild pleural effusion and none had pneumonitis. The other roentgen-ray findings generally considered characteristic of amebic abscess were relatively infrequent, and when present were usually minimal in degree (table 6).

Very bizarre roentgen findings may be demonstrated when a liver abscess ruptures into the pleural space or lung, resulting in empyema, lung abscess or bronchohepatic fistula, with or without accompanying pneumonitis. Occasionally amebic abscess of the lung complicates abscess of the liver without any apparent anatomic connection between the two. No such cases were seen in this group.

Abdomen. Enlargement of the liver was demonstrated in only four of the 15 patients who had antero-posterior films of the abdomen, yet 14 of them had enlarged tender livers on palpation. It would appear that the determination of liver size by roentgen examination in this disease is of little value.

Gall-Bladder. Six patients with subacute and chronic hepatitis were subjected to cholecystography. The gall-bladder proved to be normal in every instance.

Laboratory Findings

Blood Count. All of the abscess, 75 per cent of the acute, and a few of the subacute and chronic hepatitis cases exhibited leukocytosis. It was most marked in the abscess group (figure 6, table 7). Two patients with acute hepatitis had leukopenia on admission, but one of them subsequently developed leukocytosis. Chronic amebic abscess is also occasionally associated with a normal white blood cell count.[1]

The percentage of polymorphonuclear cells was usually only slightly elevated, an important point in differential diagnosis first noted by Rogers.[8] It was highest in the abscess group (table 7). Only one patient had a count

as high as 90 per cent. It may rise to very high levels when secondary bacterial infection occurs in an amebic abscess.

Secondary anemia is said to occur frequently in the more chronic forms of amebic abscess.[1] None was demonstrated in any of our cases.

Sedimentation Rate. An elevated sedimentation rate was found in all the abscess cases and in a high proportion of the others tested. In general it was the highest in the abscess and lowest in the chronic hepatitis group (table 7). The test was not nearly as important in diagnosis as it was in following the course of the disease under treatment.

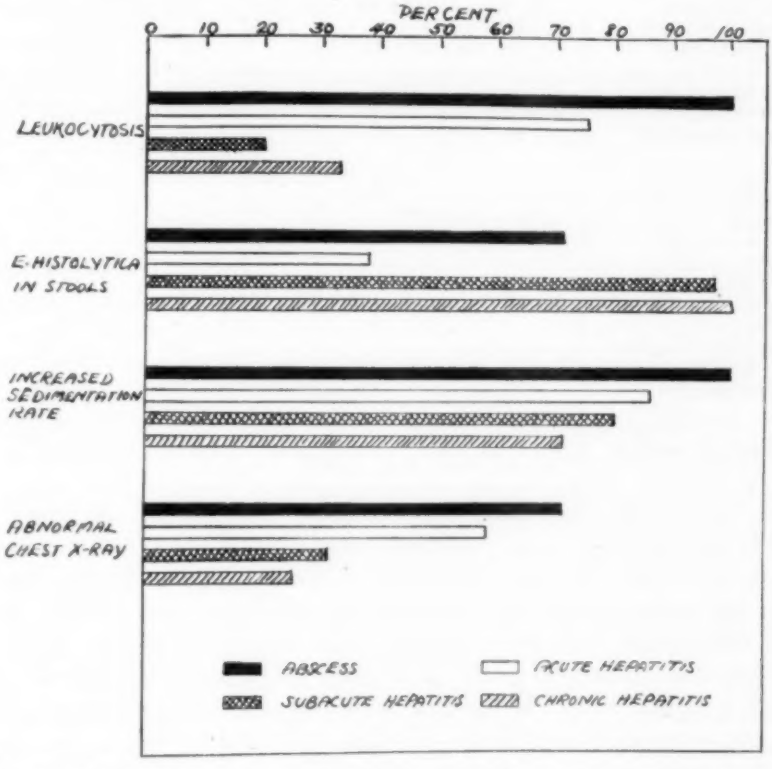

FIG. 6. Principal laboratory and roentgen-ray findings in hepatic amebiasis.

Stool Examination. E. histolytica were demonstrated in the stools of 80 per cent of the entire group. They were found in all the chronic and most of the subacute hepatitis groups, but were frequently absent in the acute hepatitis and abscess groups (figure 6, table 7). Others[1] have found the stools negative in an even higher proportion of abscess cases.

In almost every instance where the stool was positive, the characteristic actively motile trophozoites of *E. histolytica* were demonstrated.

Later experience convinced us that a much higher proportion of positive stools could be obtained by examining them following a strong saline purge.

TABLE VII

Summary of Laboratory Findings

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis	Total
White blood cell count					
Cases tested	7	16	30	6	59
W.B.C. over 10,000	7	12	6	2	27
Range	11,200–22,000	3,400–16,700	4,500–16,650	6,000–15,750	
Average	15,964	12,215	8,156	9,636	
Polymorphonuclears					
Range (per cent)	71–90	40–85	47–85	57–74	
Average (per cent)	83	72	67	66	
Sedimentation rate*					
Cases tested	4	7	25	7	43
Above 10 mm./hr.	4	6	20	5	35
Range (mm./hr.)	27–70	3–67	3–49	5–40	
Average (mm./hr.)	53	26	23	17	
Stools					
Cases tested	7	16	32	7	62
E. histolytica present	5	6	31	7	49
Albuminuria					
Cases tested	7	14	21	6	48
Number positive	3	1	0	0	4
Bile in urine					
Cases tested	0	5	7	2	14
Number positive	—	3	2	0	5
Increased urobilinogen					
Cases tested	0	4	1	1	6
Number positive	—	3	1	1	5

* Wintrobe method.

Others have made the same observation.[7] Of the 37 patients, whose normally passed stools were examined, only 24 (60 per cent) were positive, whereas all of the 25 cases examined after a purge were positive. Our technic was quite simple and consisted of examining wet smears from the second, fourth and sixth stools passed after the administration of one ounce of magnesium sulfate crystals in a glass of water. Occasional patients required a larger dose. If the first series of stools was negative, a second series was examined after a two or three day interval. In a few instances the latter were positive. Iodine-stained wet preparations were examined for cysts only when trophozoites were not found. In only one instance were cysts of *E. histolytica* demonstrated.

Urine. Albuminuria was found in four of the patients with high fever and was considered of no significance since it promptly disappeared when the fever subsided.

Traces of bile were demonstrated in five of the 14 cases tested, but in every instance the icteric index was normal.

Increased urobilinogen was demonstrated in five of the six cases tested.

Liver Function Tests. The icteric index was determined in 13 patients and was found to be slightly elevated in one case of subacute hepatitis.

Unfortunately materials were not available for carrying out any of the more elaborate procedures. Others have demonstrated impairment of function in hepatic amebiasis by the levulose tolerance[9] and the bromsulphalein tests.[13]

Treatment

In evaluating the effectiveness of treatment, the following criteria of cure were adopted: (1) complete absence of pain and fever, (2) absence of liver enlargement, (3) absence of subcostal and compression tenderness, (4) normal white blood cell count and sedimentation rate, and (5) absence of *E. histolytica* in the stools.

Treatment consisted of repeated courses of emetine until the criteria of cure were met. The emetine was supplemented with one or more courses of Diodoquin or chiniofon, followed by carbarsone, to eradicate the associated colonic amebiasis presumed to exist in all cases. None of the cases required aspiration or surgical drainage.

Results: Sixty-eight of the 69 patients treated in this manner were cured. One patient with acute hepatitis, who received a total of 22 grains of emetine, failed to meet the criteria of cure. Although he was afebrile and greatly improved clinically, his liver remained enlarged and tender. He was one of our early cases, and in the light of our present knowledge there is good reason to believe that cure could have been effected by further emetine therapy.

Sixty-one of the 69 cases were returned to full military duty. Eight were returned to the United States for further treatment. Of these, five were returned because of unrelated complicating diseases, one had a toxic myocarditis due to emetine, one had unexplained weakness and a thrombophlebitis of the saphenous vein and the last was the only case whose hepatic amebiasis had not been cured.

Six cases (two abscess and four acute hepatitis) had recrudescences of fever and pain in the hospital, which promptly responded to further emetine therapy. These occurred in our early cases before it was realized that continued emetine therapy was indicated until *all* criteria of cure were met.

Three cases of subacute hepatitis had relapses in one to two months. Reinstitution of emetine therapy effected cures in all three.

Obviously, it is difficult to compare these results with those obtained by other methods of treatment, since most reports have dealt principally with abscess and little or no effort has been made to differentiate the acute and chronic forms. In the present series more than half the cases were of the milder forms of the disease in which no mortality was to be expected. The acute forms were seen so early and treated so promptly there was little opportunity for any of the complications to develop. The principal complications of abscess, secondary bacterial infection and rupture or direct extension into the viscera or body cavities have all been shown to increase the mortality.[1, 7]

A number of abscesses, some complicated by bronchohepatic fistula, have been treated with emetine alone without any deaths.[3, 7, 8, 9] The mortality has been found to vary from 0 to 14.4 per cent with combined emetine and aspiration therapy.[7, 8] The results following surgical drainage have been the worst, the mortality rates varying between 20 and 40 per cent and even higher, although newer surgical technics have reduced these somewhat.[1] Although the differences in mortality noted between the three types of treatment are to some extent related to the fact that more severe and complicated cases require aspiration or operation, there is sufficient evidence to indicate that operation in itself increases the mortality by converting a sterile into an infected amebic abscess,[1] and there are theoretical grounds for believing that aspiration may also increase the mortality rate.

Although it is recommended that surgical drainage and aspiration be avoided, it should be noted that there are circumstances in which they may be indicated.

Emetine Dosage. Our experience has convinced us that most cases of hepatic amebiasis can be cured with emetine alone, provided the dosage is adequate. The well known cumulative action and toxic effects of emetine, however, are limiting factors that must be taken into account in planning treatment. We now feel that large doses of emetine can be given safely if adequate rest periods are included between courses.

After studying the effects of a variety of treatment schedules in our early cases, we adopted one that combines safety and effectiveness without being too time-consuming. The first course consists of 12 grains given over a 15-day period, one grain daily intramuscularly, with a three-day rest period after the sixth or ninth dose, depending on the patient's reaction to the drug. Most patients tolerate 9 grains well, but occasional patients complain of weakness and exhibit a fall in blood pressure after 6 grains. After a three-day rest period they are able to complete the 12 grain course with no ill effects.

The first course is followed by a two-week rest period, at the end of which emetine therapy is resumed. Courses of six grains each are then alternated with two-week rest periods until the criteria of cure are met. A rest period of two weeks was chosen because it proved to be sufficiently long to prevent the cumulative toxic effects of the drug. Also it was noted that considerable improvement often occurred up to two weeks after the drug was stopped, so that the total dosage of emetine could be kept down to a minimum. Where the rest periods were prolonged beyond two weeks in the face of liver tenderness, leukocytosis or an increased sedimentation rate a clinical recrudescence frequently occurred. In a few of the more acute cases the second and third courses of emetine were given at eight to 10 day intervals with no untoward effects. It may be necessary to shorten the rest periods in this manner if a recrudescence with fever occurs.

The blood pressure and pulse rate were taken twice daily and the patients were kept at complete bed rest during emetine therapy. A few complained

of weakness and exhibited a fall in blood pressure during the first course of 12 grains, but all promptly recovered during their three-day rest period and were able to resume therapy. No toxic effects were seen in the later courses of treatment, with one exception, a thin young nurse, who, through a misunderstanding, received considerably more emetine than outlined. She developed a severe myocarditis demonstrated by electrocardiography and manifested by marked weakness, hypotension and dyspnea.

Nausea and diarrhea were infrequent toxic manifestations and no patients developed neuritis.

Electrocardiograms were taken infrequently as a machine was not always available. Although, for all practical purposes, a close watch on the patient's clinical condition, pulse rate and blood pressure will disclose early myocardial damage, electrocardiograms are desirable at the beginning of each course and on the appearance of unusual cardiovascular symptoms or signs, for maximum safety during prolonged emetine therapy.

The total emetine dose required to effect cure varied with the type of hepatic amebiasis. The abscess cases required the largest doses (average 21.9 grains in 47.6 days), the acute hepatitis somewhat less (average 14.4 grains in 33.4 days), and the subacute and chronic cases the least (average 11.2 and 12.4 grains respectively in 18.1 days) (table 8).

TABLE VIII

Results of Treatment

	Abscess	Acute Hepatitis	Subacute Hepatitis	Chronic Hepatitis
Number of cases treated	7	23	32	7
Number of cases cured	7	22	32	7
Number of relapses	0	0	3	0
Emetine dosage (grains)	21.9 (12–27)	14.4 (6–24)	11.2 (6–26)	12.4 (12–15)
*Effects of treatment on:				
Fever				
Sustained fall	1.9 (1–4)	3.1 (1–12)	4.6 (1–10)	2.0 (2)
Return to normal	9.1 (5–14)	10.2 (1–59)	10.4 (1–25)	6.0 (6)
Pain and tenderness				
Diminished	4.3 (1–8)	3.4 (1–5)	5.3 (1–21)	4.7 (2–8)
Absent	29.6 (4–67)	34.4 (3–119)	17.2 (4–56)	23.6 (12–55)
Leukocytosis				
Return to normal	20.3 (4–27)	21.7 (3–65)	16.5 (10–25)	—
Sedimentation rate				
Return to normal	62.2† (58–66)	28.8 (7–42)	20.7 (7–39)	13.8 (10–17)
Total hospitalization (days)	58.6† (37–72)	66.3 (22–128)	25.8 (15–75)	31.3 (18–66)

* Figures denote days after first dose of emetine. Those within parentheses are the range of variation, the others the average.

† Apparent discrepancy between total hospital days and return of sedimentation rate to normal due to fact that sedimentation rates were determined in only 4 of the 7 cases.

The largest dose of emetine administered to any patient was 27 grains, the smallest 6 grains. One patient with acute hepatitis, and one with subacute hepatitis, were cured with 6 grains. Half of the subacute hepatitis cases were cured with less than 12 grains, usually 8 or 10. Since all three of our relapses occurred in patients who had received less than one full course, we have taken the view that 12 grains is the minimum dose any case of hepatic amebiasis should receive.

Most of the cases of amebic abscess in the literature, cured with emetine alone, received between 10 and 12 grains of emetine, although Berne [7] reports having used up to 24 grains. The relatively small doses employed suggest that these abscesses were of the early acute type, such as was seen in our series. Payne's recent paper [3] would seem to indicate that emetine alone is equally effective in the larger more chronic abscesses, since his 24 cases required an average of 36 grains given over a period of 108 days. One of his patients received 60 grains in 120 days.

Response to Emetine (table 8). The response to emetine in our cases was usually so dramatic it was considered diagnostic of the disease.

In two to five days there was usually an appreciable fall in temperature and diminution in liver pain and tenderness. In many patients marked improvement was noted after as little as one grain of emetine. In a few the response was very slow.

The temperature was usually normal by the ninth or tenth day, but liver pain and leukocytosis took considerably longer to clear up completely.

The sedimentation rate took the longest to reach normal, often remaining elevated after the other criteria of cure had been met. This was especially true of the abscess cases in whom the sedimentation rates were elevated for an average of 62.2 days.

Total hospitalization averaged approximately two months in abscess and acute hepatitis and approximately one month in the subacute and chronic hepatitis groups.

Indications for Aspiration. It has been clearly shown that emetine in sufficient dosage is the prime factor in the cure of uncomplicated amebic liver abscess. Aspiration of its contents removes a foreign body factor which may be of importance in some cases.[7] The advantages to be derived from aspiration are confirmatory evidence of the diagnosis, a shortened convalescence, early detection of secondary bacterial infection, and possibly prevention of rupture or extension into neighboring structures. Against these must be weighed the possible dangers, namely, hemorrhage or rupture into the serosal cavities and the introduction of secondary bacterial infection.

In most cases the prompt response to emetine therapy is sufficient evidence to confirm the diagnosis based on clinical findings. Comparative studies are not available to indicate that convalescence is actually shortened by aspiration, although such an assumption seems reasonable. Nevertheless, the dangers would appear to outweigh the possible advantages of a shortened clinical course.

It has seemed to us, therefore, that the indications for aspiration are: (1) failure of the patient to show any improvement after a full course of 12 grains of emetine, and (2) clinical or roentgen evidence that an abscess located near the surface of the liver is getting larger under emetine therapy.

The technic of aspiration of the liver has been described elsewhere.[17] If the aspirated contents are found to contain bacteria, emetine therapy should be supplemented with one of the sulfonamides or penicillin. A case of chronic amebic abscess with secondary *beta hemolytic streptococcus* infection has recently been successfully treated with aspiration followed by the instillation of penicillin through a fine catheter.[18] The injection of emetine into the abscess cavity[19] does not appear to offer any advantages over the intramuscular route.

Indications for Surgical Drainage. Before the advent of the sulfonamides and penicillin, evidence of secondary bacterial infection was an indication for operation. Bacterial infection is an infrequent complication [8] so that relatively little experience with these new drugs has been accumulated, but there is reason to believe that many cases will be cured with aspiration and chemotherapy, and they should be tried before operation is attempted.

Aspiration of superficially located abscesses in the left lobe of the liver has been found hazardous and surgical drainage is usually recommended when emetine therapy alone fails.[8] Fortunately the operative risk is much lower in these than in right lobe abscesses.

Acute rupture of an abscess into one of the serous cavities is usually an indication for surgical drainage, especially when it occurs into the peritoneum or pericardium. Rupture into the pleural space does not necessarily require surgical drainage, unless the abscess contents are secondarily infected. Simple aspiration plus emetine therapy frequently effects a cure.

Ochsner and De Bakey's [1] extraserous approach to the liver would appear to be the method of choice where operation is contemplated. Since operation invariably results in secondary bacterial infection of the abscess, sulfonamides or penicillin should always be administered. Obviously a full course of emetine is also indicated, preferably preoperatively if feasible.

Diagnosis

The early diagnosis of hepatic amebiasis depends chiefly on a careful analysis of the patient's symptoms and physical findings. Roentgen-ray and laboratory examinations often yield helpful collateral evidence but are rarely diagnostic. Confirmation of the diagnosis usually rests on the clear-cut specific response to emetine therapy. More direct confirmation requires the demonstration of amebae in the liver, possibly only in the later stages of the disease when an abscess has developed, and even then amebae are often not found on aspiration. The diagnostic value of a therapeutic trial of emetine in this disease has been amply confirmed.[8, 20, 21]

The clinical picture of hepatic amebiasis may simulate a great variety of diseases, but they can usually be differentiated without much difficulty.

Most errors in diagnosis are due to a failure to consider the possibility of hepatic amebiasis. This is especially true in the temperate zone where amebiasis is generally regarded as a tropical disease. Numerous studies have indicated that amebiasis is by no means a rare disease in the temperate zone.[1]

The conditions to be considered in the differential diagnosis of hepatic amebiasis will depend on the stage of the disease, the predominant symptoms and the presence or absence of complications. In general, they may be grouped as follows: (1) diseases of the right upper quadrant of the abdomen, (2) pulmonary diseases and (3) primary febrile illnesses.

An analysis of the initial diagnoses made on our cases gives some indication of the diagnostic problems involved (table 9). Attention should be

TABLE IX

Diagnoses Made on Admission to the Hospital

	Abscess and Acute Hepatitis (23 Cases)*	Subacute and Chronic Hepatitis (39 Cases)*
Right upper quadrant syndrome	*12*	*39*
Hepatitis		
Amebic	5	29
Unclassified	4	6
Cholecystitis	2	1
Gastritis	1	0
Renal calculus	0	1
Pyelitis	0	1
Herpes zoster	0	1
Pulmonary syndrome	*7*	*4*
Pleurisy	0	4
Pneumonia	3	0
Upper respiratory infection	4	0
Primary acute febrile illness	*7*	*2*
Malaria	3	2
Typhoid	3	0
Dengue	1	0
Diarrheal diseases	*6*	*31*
Amebic dysentery	3	30
Acute enteritis	3	1

* Multiple diagnoses account for the discrepancy between the number of cases and the number of diagnoses.

drawn to the fact that the medical officers who saw these patients on admission were keenly aware of the amebiasis problem and were on the lookout for hepatic cases. Multiple diagnoses were common, so that statistical analysis is difficult, but a few important points stand out that are worthy of consideration.

The clinical picture was sufficiently clear to suggest disease in the right upper quadrant of the abdomen in 51 of the 62 cases, and in 44 of these it could be localized in the liver. In 34 the correct diagnosis was made before any laboratory or roentgen-ray examinations were carried out. Liver disease was suspected in almost all of the subacute and chronic hepatitis, but in only one-third of the abscess and acute hepatitis groups.

A diagnosis of pulmonary disease was made in 11 of the 62 cases. It was made in one third of the abscess and acute hepatitis groups and in only four of the 39 subacute and chronic hepatitis cases. Pneumonia or upper respiratory infection was suspected in the former and pleurisy in the latter.

One third of the abscess and acute hepatitis cases were thought to have one of the primary acute febrile illnesses—malaria, typhoid or dengue. Two of the subacute hepatitis groups with fever were diagnosed malaria.

In almost every instance where the diagnosis of hepatic amebiasis was not considered on admission, reëxamination revealed painful enlargement or compression tenderness of the liver or both, indicating the true nature of the disease. The demonstration of *E. histolytica* in the stools added weight to the diagnosis of hepatic amebiasis, but had to be regarded with suspicion since the incidence of amebiasis in all our troops was so high. The absence of *E. histolytica* by no means excluded the diagnosis. Leukocytosis with a relatively low polymorphonuclear count was a helpful point in differentiating hepatic amebiasis from pneumonia and the other acute febrile illnesses. Roentgen-ray examination was particularly useful in excluding pneumonia, but indicated liver disease in only a few instances.

The diagnosis was much simpler, on the whole, in the subacute and chronic hepatic groups. The one disease that might have been confusing, infectious hepatitis, actually presented very little difficulty. The absence of jaundice, anorexia, indigestion, splenomegaly and leukopenia, the infrequent occurrence of nausea and the presence of compression tenderness of the liver favored an amebic etiology and the prompt response to emetine therapy confirmed it. The ineffectiveness of emetine therapy in infectious hepatitis was amply demonstrated in a number of these patients who were found to have *E. histolytica* in their stools. A full course of emetine had no effect on their symptoms or the liver findings, and they ran the usual four to eight week course of this disease.

Of the three cases with involvement of the left lobe of the liver, two were correctly diagnosed on admission and they responded promptly to emetine therapy. The third, an abscess, was thought to have an early pneumonia of the left lower lobe and was treated with sulfathiazole. Chest pain, fever and leukocytosis increased under this form of therapy. Reëxamination of the patient on the fourth day disclosed the fact that the pain was located beneath the left costal margin, radiated to the chest and had all the other characteristics of liver pain. The liver was found to be enlarged and tender with marked compression tenderness and there was a mass beneath the left costal margin. The stools were positive for *E. histolytica*. Rapid recovery followed the institution of emetine therapy.

A secondary diagnosis of amebic dysentery was made on admission in 33 of the 62 cases. Thirty of these fell into the subacute and chronic hepatitis groups, in which, it will be recalled, diarrhea was such a prominent symptom.

A diagnosis of hepatic amebiasis was made fairly promptly in most of the cases. An average of 4.2 days elapsed between admission and the institution of emetine therapy. In 28 cases treatment was started within 24 hours. The longest delay was 20 days.

Chronic amebic abscess, not encountered in this series, presents a number of diagnostic difficulties not mentioned, especially when complicated by extension to neighboring structures. The right upper quadrant syndrome may simulate carcinoma of the liver, stomach or gall-bladder, cirrhosis, amyloid or ecchinococcus disease of the liver, hepar lobatum, pyogenic abscess of the liver and abscess complicating peptic ulcer or cholecystitis. The pulmonary syndrome may simulate post-pneumonic empyema, tuberculous pleural effusion, pyogenic lung abscess and bronchogenic carcinoma.[7, 21]

Summary and Conclusions

1. Sixty-nine cases of amebiasis of the liver were encountered in two U. S. Army hospitals in India over a period of 22 months. The clinical features of 62 and the results of treatment in all 69 were discussed.

2. The cases fell into four distinct groups which could be readily differentiated clinically: (1) acute abscess, (2) acute hepatitis, (3) subacute hepatitis and (4) chronic hepatitis. The clinical features and laboratory findings in each were correlated with the known facts about the pathology of the disease. The findings were compared with those seen in chronic amebic abscess, the form of the disease usually described.

3. Emetine therapy alone cured 68 of the 69 cases. One patient was improved but failed to meet the rigid criteria of cure laid down. The necessity for prolonged emetine therapy was stressed and a safe dosage schedule outlined.

4. The clinical classification of hepatic amebiasis makes for a better understanding of the underlying pathology, calls attention to the less commonly recognized forms of the disease and gives some indication of the amount and type of treatment required.

5. The early diagnosis of hepatic amebiasis depends chiefly on a careful analysis of the symptoms and physical findings. Roentgen-ray and laboratory examinations yield helpful collateral evidence, but are rarely diagnostic. Confirmation usually rests on the specific response to emetine therapy. The demonstration of amebae in the liver is possible only in the late stages of the disease.

6. Emetine is the treatment of choice in all forms of hepatic amebiasis. Aspiration and surgical drainage are indicated under special circumstances, especially in late abscess cases.

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SOME COMMON CONDITIONS, NOT DUE TO PRIMARY HEART DISEASE, THAT MAY BE ASSOCIATED WITH CHANGES IN THE ELECTROCARDIOGRAM *

By WILLIS SENSENBACH, M.D., *High Point, North Carolina*

DURING the past 25 years, the science of electrocardiography has been developed to the point where it has become an important and valuable adjunct to clinical medicine. In more recent years its use in clinical medicine has become widespread. Coincidentally, and perhaps inevitably, with the increased application of electrocardiography, there has developed a tendency towards serious misuse of this valuable and useful method. The major reason for the abuse of the electrocardiogram is that its limitations have not been properly recognized. The frequency with which serious errors in medicine are made because of unjustified conclusions reached from interpretation of electrocardiograms is alarming, and the situation cannot be expected to improve until there is a more general realization of the limitations of electrocardiography. It is my purpose to point out briefly some conditions in which the electrocardiogram may be of value and to indicate in somewhat more detail some of the limitations of the method.

The electrocardiogram is of great value in the detection and classification of the cardiac arrhythmias. Although it is true that in most instances a correct clinicial diagnosis of the arrhythmias can be made at the bedside, there are occasional cases in which a correct diagnosis must depend on electrocardiographic findings. This is true when there is auricular flutter with constant auriculoventricular block and a regular ventricular rhythm at a relatively slow rate, and when no clue can be obtained from physical examination because the patient is too ill to be exercised. When there is a totally irregular rhythm due to many auricular or ventricular premature beats, it may be impossible clinically to differentiate with certainty such an arrhythmia from auricular fibrillation. A diagnosis of ventricular tachycardia, although often suspected clinically, always requires electrocardiographic confirmation. Finally, even when one can be quite sure of the clinical diagnosis of an arrhythmia, electrocardiographic confirmation is desirable and comforting.

The electrocardiogram may be of real value in the recognition of myocardial infarction. In most instances of acute myocardial infarction, the electrocardiographic tracing will not only reveal the presence of the infarction but may allow one to localize it with a reasonable degree of certainty to the anterior, posterior or lateral wall of the ventricle. The electrocardiogram will be of value, not only in the recognition of myocardial infarction,

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From the Department of Medicine, Southwestern Medical College; St. Paul's Hospital and The Methodist Hospital, Dallas, Texas.

but also in following the course of the disease. Serial tracings taken during the course of an acute myocardial infarction may be useful in following the progress of the disease and may give helpful information in regard to the healing of the infarction. Furthermore, it may be possible to identify old and previously unrecognized cases of myocardial infarction through the persistence of certain residual changes in the electrocardiogram. In this respect, however, its value is not great, since certain extracardiac influences may produce changes of a similar nature.

The electrocardiogram may be of value during the course of certain systemic diseases, such as rheumatic fever, trichinosis or diphtheria, to indicate when the heart has become involved. Electrocardiographic evidence in such instances may be the only evidence obtainable to indicate if and when cardiac involvement has occurred.

Less frequently the electrocardiogram may be of value in revealing or making one suspicious that a patient has been taking certain drugs, notably digitalis. At times, when one cannot be certain from the history that a patient has been taking digitalis, an electrocardiogram may reveal the typical findings of digitalis effect. The presence of a normal electrocardiogram, however, in such a case is not positive proof that the patient has not been taking digitalis. The diagnosis of digitalis intoxication, as a rule, depends on clinical findings and is not information that can be gleaned from the electrocardiogram. Although the changes in the electrocardiogram due to the effect of digitalis may at times be helpful, in many instances these changes are misinterpreted as being evidence of myocardial disease. When it is important to determine whether or not the changes in a given electrocardiogram are due to myocardial disease or to the effect of digitalis, the drug should be withdrawn, and if the changes in question are due to its effect, they should disappear within a period of three weeks. Changes due to digitalis will usually disappear more promptly, but it should be remembered that they may sometimes persist for as long as three weeks after the drug has been discontinued.

The electrocardiogram, then, may be of great value in the detection and classification of the cardiac arrhythmias and in the recognition of acute myocardial infarction. It may also be of value in determining when the heart has become involved in the course of certain systemic diseases and in revealing the influence of certain drugs, principally digitalis.

With this brief discussion of the value of electrocardiography as an introduction, we may discuss in somewhat more detail some of the limitations of the method. It should be stressed from the outset that as compared to other methods of examination the electrocardiogram provides very little information as to function of the heart or as to prognosis. The electrocardiogram is often entirely normal in individuals suffering from severe heart disease and advanced congestive heart failure. Many patients with angina pectoris on slightest exertion and severe coronary sclerosis will exhibit a normal electrocardiogram while at rest. In those patients with severe coro-

nary artery disease and normal resting electrocardiograms, exercise will effect transient changes in the tracing which reveal the coronary disease in a fairly large number of cases. There remains, however, an appreciable number of patients with severe coronary artery disease and angina pectoris who have normal electrocardiograms, even immediately after exercise. Such patients have obvious functional impairment, yet exhibit no abnormal changes in the electrocardiogram. On the other hand, there may be striking changes in the electrocardiogram in the absence of heart disease and when there is no functional impairment of the heart. It is clear, then, that as far as function is concerned, the electrocardiogram is not a reliable measuring rod and if depended upon, may be dangerously misleading. It is equally incorrect to look to the electrocardiogram for information regarding prognosis in a patient with heart disease. In many individuals with serious heart disease who have had one or more myocardial infarctions in the past the changes in the electrocardiogram will have completely disappeared after the infarctions have healed. Such individuals may have marked coronary artery sclerosis, yet no clue as to the serious nature of the heart disease may be gained from a study of the single electrocardiographic tracing. On the other hand, there may be striking changes in the electrocardiogram in certain individuals who have no evidence of heart disease and who may be expected to live for many years. The Wolff-Parkinson-White syndrome, where there are the changes of bundle branch block with a short PR interval, is an example of such a condition. A serious error in prognosis would be made by one who interpreted these changes as indicating poor prognosis or impairment of function, for in such individuals the heart is normal, the bizarre findings in the electrocardiogram being due to short circuiting of the conduction impulse through the bundle of Kent.

A third cause for error in the interpretation of the electrocardiogram lies in an adherence to too rigid criteria for normality in the electrocardiographic tracing. Recent reports of Stewart and Manning[31] and Graybiel, McFarland, Gates and Webster,[13] who studied electrocardiograms made on large numbers of healthy young adults in the Armed Forces, show clearly that our present standards of normality in the electrocardiogram are in need of revision. For example, the term "sinus bradycardia" is usually used to denote rates below 60. Graybiel and his coworkers found that one-third of their cases had rates between 50 and 60. They believe the term "sinus bradycardia" should be reserved for rates below 45. Notching of the P-wave, usually considered abnormal, occurred in 27 per cent of their cases of normal healthy males. The upper limit of normality in the PR interval is usually considered to be between .18 and .20 second, depending on the age of the individual. In the series of Graybiel et al. the PR interval was .19 second in 19 cases, .20 second in 33 cases, .21 second in four cases, .22 second in eight cases and .24, .25, .26 and .28 second in one case each. Four cases in the Stewart and Manning series presented a PR interval of over .24 second, the longest one of which was .36 second. According to present

standards .10 second is the upper limit of normal for the QRS interval. In the combined series of 1500 cases there was a QRS interval of over .10 second in 47 cases. In one case of Grabiel et al. the QRS interval was .13 second. They concluded that a QRS interval as long as .13 second may be observed in young persons without evidence of heart disease and that a QRS interval of .11 second is found with sufficient frequency in young, healthy adults to suggest that it is not necessarily of pathological significance. Notching and slurring of the QRS complex, often considered of pathological significance, occurred in the total of 1500 cases 36 times in Lead I, 39 times in Lead II and in 210 cases in Lead III. An amplitude of the QRS complex no greater than 5 mm. in the standard limb leads occurred in 16 cases. Left and right axis deviation occurred with sufficient frequency to show that deviation of the electrical axis in itself is not necessarily of pathological significance. There were 95 instances of left axis deviation and 64 instances of right axis deviation occurring among the 1500 normal, healthy adults.

Displacement of the ST segment of more than 1 mm. was a rare occurrence in this series of normal healthy adults. The ST segment was displaced upward more than 1 mm. in Lead I in 6 instances, in Lead II in 35 instances, and in Lead III in 7 instances. Downward displacement of more than 1 mm. occurred once in Lead I, not at all in Lead II, and three times in Lead III.

In the entire series of 1500 cases there was no instance of an inverted or diphasic T_1. In two instances T_2 was inverted, and in two instances it was diphasic. T_1, on the other hand, was inverted or diphasic in one-fifth of all the cases of Graybiel, et al. and in 28 per cent of Stewart and Manning's cases.

These results show that "the range of variation in the electrocardiogram of normal young airmen is considerably greater than the present standards would lead one to expect, and a relatively large number of records show characteristics which hitherto have been considered diagnostic of heart disease". The obvious conclusion is that the normal in electrocardiography extends well into what has been commonly regarded as the abnormal range. These results emphasize the great individual variation in electrocardiographic pattern and the wide range of normal values, so that we are coming to realize that many changes in the electrocardiogram that have previously been considered definitely abnormal, in a great many instances actually are not. Until the present criteria for normality are revised these minor changes that may occur in normal individuals should be disregarded when there is lack of clinical correlation. For that matter, any electrocardiographic changes should be viewed with skepticism when the findings cannot be correlated clinically with the patient.

Most of the serious errors of interpretation of the electrocardiogram may be found in the interpretation of the changes that occur in the ventricular complex, including the ST segment and T-wave. There is fairly widespread belief that the changes in this particular part of the electrocardio-

gram specifically indicate myocardial disease or disease of the coronary arteries. This misconception has undoubtedly led to the more serious errors of electrocardiographic interpretation and is in large part due to a failure of recognition of the non-specificity of changes in this portion of the tracing. In order to emphasize the lack of specificity of these changes, I wish to present a list of some of the more common conditions, not due to primary disease of the heart, which may bring about changes in the electrocardiogram similar to those commonly attributed to coronary sclerosis and diffuse myocardial disease.

1. *Drugs:* Many drugs produce changes in the electrocardiogram. The effect of digitalis is well known, as is that of quinidine. Less well recognized is the effect of other drugs. The anti-malarial drugs, plasmochin, atabrine and quinine, cause electrocardiographic changes.[19] Plasmochin increases the amplitude of the QRS complex and T-wave. In some cases it causes elevation of the ST segment which may stimulate, in some degree, those changes which occur after a coronary thrombosis. Atabrine, on the other hand, decreases the amplitude of the QRS and the T-waves and restores the ST segment to the iso-electric level after it has been elevated by plasmochin. Quinine has a similar effect to atabrine, but to a lesser degree. Adrenalin, ergotamine tartrate, atropine, emetine and mecholyl [16, 18] are other drugs that may affect the ST segment and the T-wave in the electrocardiogram. Inhalation of tobacco smoke brings about an increase in the rate of the heart and not infrequently causes lowering or inversion of the T-waves.[14] These changes are transient and disappear promptly when the subject stops smoking. They are due to the effect of the nicotine in the tobacco smoke.

It is important, then, that electrocardiograms be interpreted with a knowledge of the drugs the patient has been taking so that changes caused by such drugs may not be mistakenly attributed to disease of the heart. The changes in the electrocardiogram due to drugs disappear after the drugs are withdrawn.

2 *Exercise:* Excessive exercise in normal individuals will produce depression of the ST segments and flattening or inversion of the T-waves (figure 1).[18, 29] These changes are most likely related to the reduction in coronary blood flow incident to the tachycardia that occurs with excessive exercise and are quite transient and disappear promptly with the decline in rate of the heart. For the same reason similar changes may occur in the electrocardiogram in patients who have paroxysmal auricular tachycardia or paroxysmal auricular fibrillation. These changes may be noted after the subsidence of the attack, and unless the attack is of extremely long duration, they are transient and disappear within a few hours or days after the tachycardia is terminated.

3. *Acute Infection:* Inversion of the T-wave and changes in the ST segment have been described as occurring during the course of various acute infections: pneumonia, trichinosis, diphtheria, typhoid fever, typhus fever, influenza, periarteritis nodosa, undulant fever, and pulmonary tuberculosis.[23]

These changes are transient and disappear with the subsidence of the acute infectious process.

4. *Pericarditis:* Fairly characteristic electrocardiographic changes may appear in acute and in chronic pericarditis. It is permissible to consider

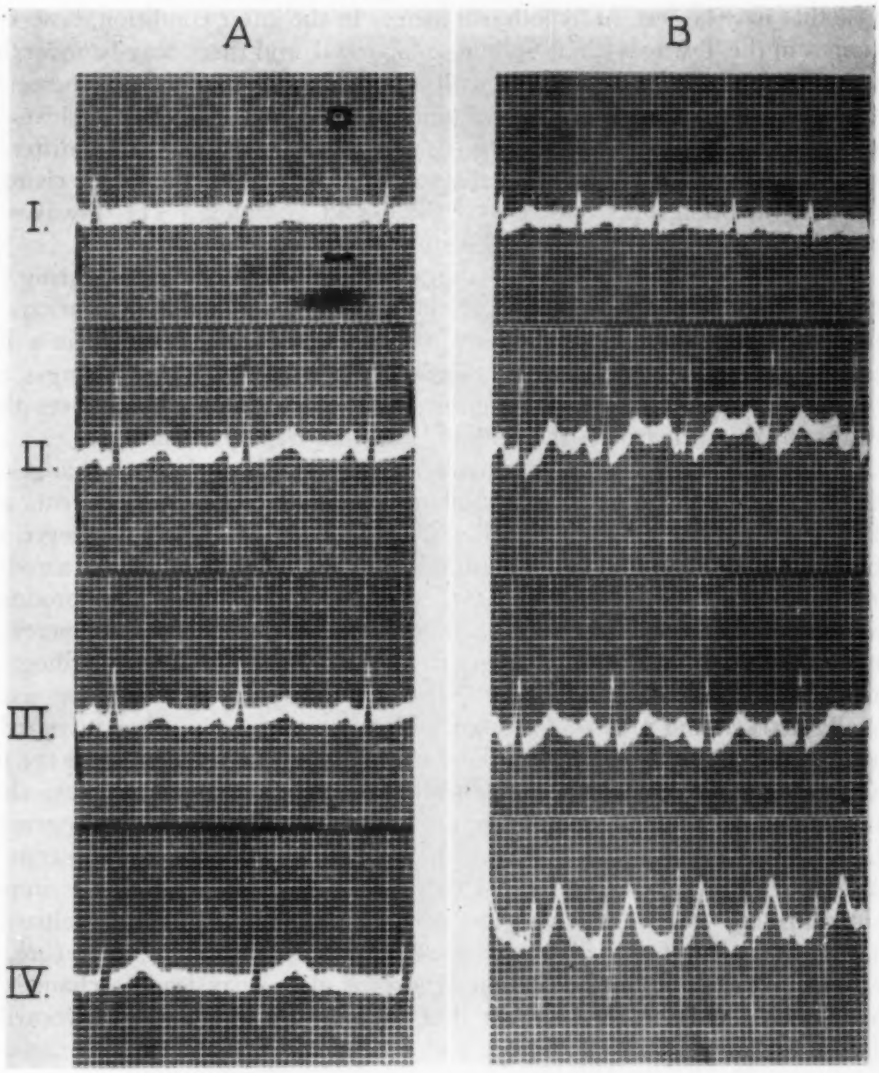

FIG. 1. A. Electrocardiogram made on a normal, healthy medical student at rest. B. Record made immediately after exercise.

pericarditis as an extra-cardiac lesion, and it is considered so here because the electrocardiographic changes, either in chronic or acute pericarditis, may be similar to those caused by diffuse myocardial disease resulting from coronary arteriosclerosis. In both acute and chronic pericarditis, the clinical picture

is usually so clearcut as to preclude the necessity for electrocardiographic evidence in differentiating the two conditions.

5. *Metabolic Disorders:* In simple obesity there may be changes in the electrocardiogram, usually characterized by low amplitude of the QRS complex and of the T-wave. These changes are similar in many respects to those that may be seen in hypothyroidism. In the latter condition, however, changes in the T-waves are usually more marked, and there may be inversion of these waves in all leads occasionally with depression of the ST segments. Following thyroid medication the amplitude of the QRST complexes is increased, and the record is restored to normal. Changes of a different nature have been described in hyperthyroidism,[8] with again the major changes occurring in the terminal portion of the QRST complex. The T-waves in hyperthyroidism are often increased in amplitude.

Clagett has described minor changes in the electrocardiogram during the course of artificial fever therapy.[4] The changes are mainly variations in amplitude of the various components of the electrocardiogram, but in a few instances there may be slight ST segment depression. These changes are transient, and are considered insignificant by the author, who believes they are due to the tachycardia that accompanies the hyperpyrexia.

Alterations in the acid-base balance in the body may lead to changes in the electrocardiogram that may simulate those due to coronary sclerosis and diffuse myocardial disease. Alkalosis,[2, 20, 31] produced either by overventilation or by the ingestion of sodium bicarbonate, is accompanied by a reduction in the amplitude of the T-waves. Acidosis, on the other hand, produced experimentally by the ingestion of ammonium chloride, causes an increased amplitude of the T-waves. Changes that may occur in the electrocardiogram during the course of the hyperventilation syndrome, for example, are occasionally marked and may be confused with those that occur after myocardial infarction.[31] It is believed that these changes are due to changes in the pH of the blood, since alkalosis brought about by other means may cause similar changes in the electrocardiogram. The fact that electrocardiographic changes similar to those occurring in myocardial infarction may occur in patients with anxiety neurosis and the hyperventilation syndrome is important, since most of them have chest pain which, without careful evaluation, may be mistaken for angina pectoris. It is very important, therefore, to recognize that the hyperventilation syndrome alone may lead to changes in the T-waves and the ST segment that simulate those found in myocardial disease and myocardial infarction.

Case 1. A young married woman entered the hospital complaining of severe shortness of breath and "heart trouble" of a few weeks' duration. She was greatly disturbed emotionally and hyperventilated almost continuously while awake. Except for moderate obesity the physical examination was normal. The heart was not enlarged, and there were no murmurs. The blood pressure was normal. Roentgen-ray and fluoroscopy of the heart revealed no abnormalities in the size or shape of the cardiac silhouette. The electrocardiogram (figure 2) was distinctly abnormal, the most marked change being in Lead II, where the T-wave was sharply inverted.

Bellet and Dyer [3] observed electrocardiographic changes in all of their cases of diabetic acidosis. The chief alterations observed were prolongation of the QT interval, lowering or inversion of T-waves and depression of ST segments. These changes were transient and were most marked, not during coma, but about 24 hours later when the patients were clinically improved.

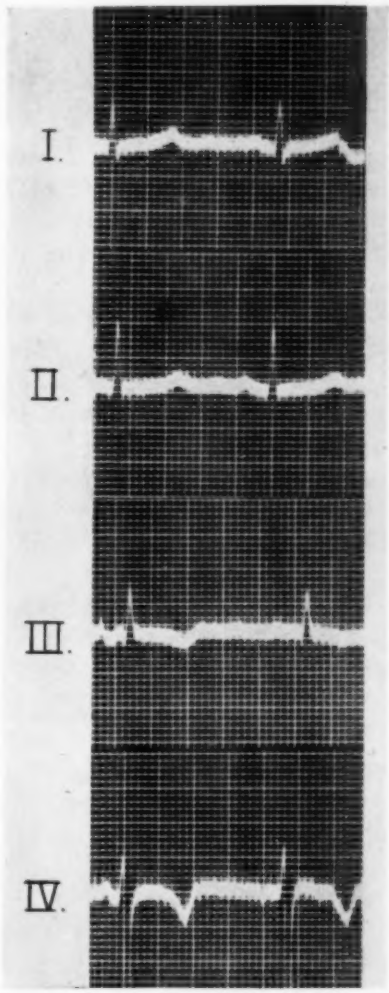

FIG. 2. Abnormal electrocardiogram with T_4 inversion in a patient with a marked anxiety state and hyperventilation syndrome.

One patient whose acidosis was non-diabetic in origin exhibited similar changes in the electrocardiogram.

The administration of insulin in amounts sufficient to cause hypoglycemia will produce changes similar to those found in diabetic acidosis. These changes not only occur in patients who have diabetes, but have been noted in

non-diabetic patients who have been subjected to insulin shock therapy. In a few persons with spontaneous hypoglycemia or hyperinsulinism similar changes have occurred.

Case 2. A 39 year old male had had numerous attacks of constrictive precordial pain associated with numbness in the left arm. The pain varied from mild to severe, and lasted from one to two hours. There was no relationship to exertion, and no attack had occurred within two hours after a meal. The physical examination was negative. No pain or electrocardiographic changes could be induced by exertion. However, a typical attack of pain and marked electrocardiographic changes (figure 3) could be induced by insulin. The attacks were prevented by a low carbohydrate, high protein diet.

Harrison and Finks [17] report the case of a 27 year old female who had typical attacks of angina pectoris, and whose attacks were not related to exertion, but could be induced by insulin and relieved by either nitroglycerin or orange juice. During the attacks elevation of the ST segments in the electrocardiogram was noted.

Fox and Messeloff [8] have described transient electrocardiographic changes occurring during the course of serum sickness. In their case, the QRS complex was diminished in amplitude, as was the T-wave in Leads II, III and IV. There were only minor ST segment changes. In 10 days the electrocardiogram had become normal.

Electrocardiographic changes are not uncommon in certain vitamin deficiency diseases.[26, 27] In beriberi and in minor grades of vitamin B_1 deficiency, T-wave abnormalities, as well as low amplitude of the QRS complexes, have been described. The electrocardiographic changes in pellagra are mainly characterized by lowering and inversion of the T-waves. The administration of thiamin chloride or nicotinic acid results in a prompt return of the electrocardiogram to normal. Rachmilewitz and Braun [27] proposed that the changes in the electrocardiogram that may occur during the course of pellagra are metabolic in origin as a result of a coenzyme deficiency in the heart muscle. This impression was confirmed by Govier [12] who found that coenzyme 1 is reduced by 70 per cent to 83 per cent of normal in cardiac muscle rendered ischemic by coronary artery ligation. Nicotinamide given intravenously before coronary ligation protected to a great extent against the breakdown of coenzyme 1.

Electrocardiographic changes are frequently observed in the anemias of both the acute and chronic types. In the chronic anemias, such as untreated pernicious anemia or sickle cell anemia, the changes may be due to actual changes in the myocardium since many such patients also have cardiac enlargement. Usually, unless the anemia is of very long duration, the electrocardiographic changes will disappear when the anemia is corrected. Scherf and Klotz [28] have described electrocardiographic changes occurring in the acute anemia due to sudden blood loss. These changes were characterized by lowering to inversion of the T-waves and depression of the ST segments. Slightly lowered amplitude of the QRS complex was occasionally observed.

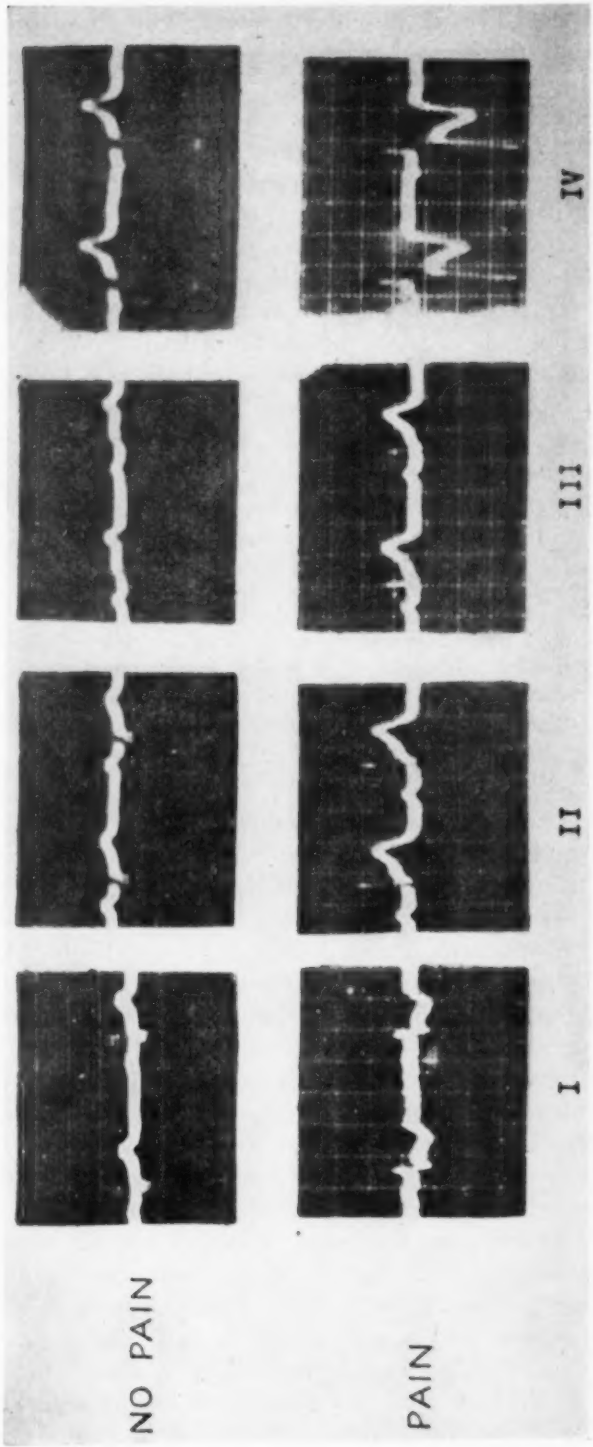

FIG. 3. These electrocardiograms show the marked ST segment displacement that may be induced by insulin. See text, case 3.

The changes developed in the absence of shock, without severe anemia and were independent of the hemoglobin level. They disappeared in two to nine days.

Carbon monoxide poisoning may be associated with changes in the electrocardiogram.[30] The commonest changes are lowering or inversion of the T-waves, with or without slight displacement of the ST segments. Intraventricular block has been reported, but this occurs more rarely.

6. *Renal Disease:* Variations in the serum potassium level may lead to changes in the electrocardiogram.[4, 20] In patients with uremia and potassium retention, intraventricular conduction defects have been described, along with increased amplitude of the T-waves in all leads. With potassium depletion, decreased amplitude of the T-waves and slight ST segment depression may occur. These changes disappear after the potassium deficit in the serum is corrected. Electrocardiographic changes occur in acute glomerulonephritis in a high percentage of cases.[1] The most striking changes are seen in the T-waves, with low amplitude to inversion, and there may also be depression of the ST segments. In some cases the changes may be strikingly similar to those due to acute myocardial infarction.

Case 3. A 14 year old girl entered the hospital with the characteristic findings of acute glomerulonephritis. She was critically ill at the time of admission, and remained so for a period of two weeks when clinical improvement began. An interesting series of electrocardiograms was obtained (figure 4), revealing changes very similar to those that occur in myocardial infarction. As the patient improved clinically, the electrocardiogram changed so that by the time the patient was discharged from the hospital it had become almost normal.

7. *Acute Upper Abdominal Conditions:* Acute inflammatory lesions in the upper abdomen may be associated with electrocardiographic changes that may be similar in many respects to those caused by disease of the coronary arteries. Such electrocardiographic changes have been described in acute pancreatitis,[10, 11, 15] in uncomplicated disease of the gall-bladder,[6, 7, 24] bleeding peptic ulcer,[28] ruptured peptic ulcer.[25] These changes are transient and disappear after the removal of the acute abdominal focus. It is important that this fact be recognized, since there is occasionally difficulty in determining whether severe upper abdominal pain is arising from below or above the diaphragm. Unless one is aware of the fact that electrocardiographic changes may occur in certain acute upper abdominal lesions, he may be misled on the basis of electrocardiographic findings into attributing the origin of the pain to the heart rather than to the abdomen.

8. *Pulmonary Embolism:* Embolus to a large branch of the pulmonary artery may be associated with changes in the electrocardiogram which may resemble those due to coronary sclerosis. Slight depression of the ST segments and inversion of the T-waves, especially of T_2 and T_3, may occur. A deep S-wave in Lead I and Q-wave in Lead III also often appear.

9. *Autonomic Nervous System Imbalance:* Certain patients with neurocirculatory asthenia may show T-wave inversion in Leads II and III.[22, 33]

These findings tend to vary from time to time so that occasionally the T-waves may be upright, having previously been inverted. Increased amplitude of the T-wave may also occur in this disease.

There is evidence to indicate that fear may cause changes in the electrocardiogram in persons with normal hearts (figure 5). Mainzer and Krause [23] made electrocardiograms on patients on the operating table immediately before the induction of a general anesthetic. Abnormal electrocardiographic records, as compared with a tracing made on the previous day, were obtained

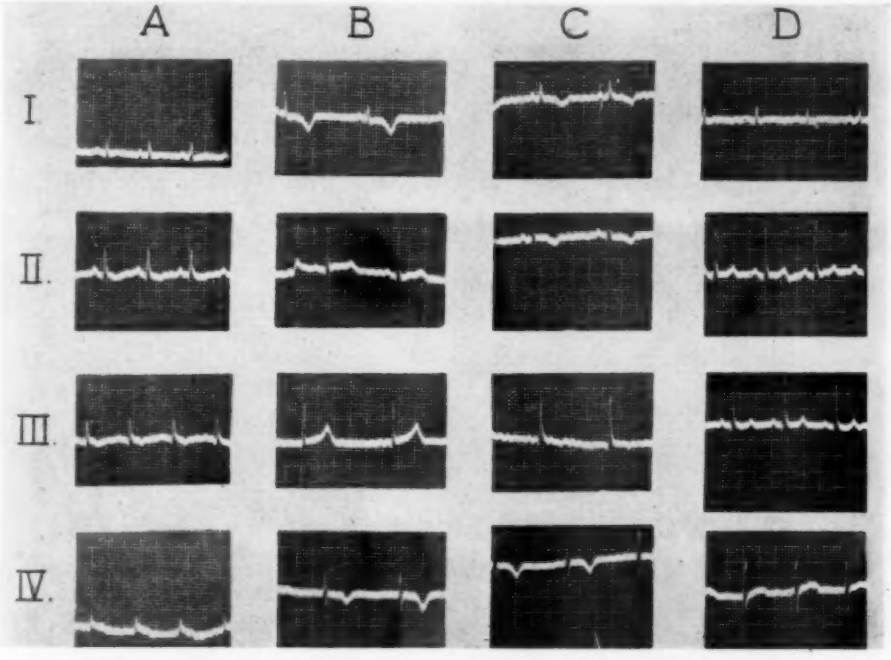

FIG. 4. A. Sept. 22, 1943, shortly after admission to the hospital.
B. Oct. 4, 1943, the patient still critically ill, blood pressure elevated, marked nitrogen retention.
C. Oct. 8, 1943, at this time clinical improvement has begun.
D. Oct. 25, 1943, almost complete clinical recovery. The electrocardiogram also is now almost normal.

in two-fifths of their 53 cases. The changes noted consisted in depression of the ST segment, flattening or inversion of the T-waves, these changes being similar to those appearing in coronary insufficiency. In other cases, increased amplitude of the P-waves and the T-waves with sharply pointed P- and T-waves was noted. These changes are similar to those that may be seen in neurocirculatory asthenia.

The foregoing would seem to indicate, then, that the changes in the terminal portion of the QRST complex, so often considered specific of myocardial disease, are far from being so, since we are able to present a list, ad-

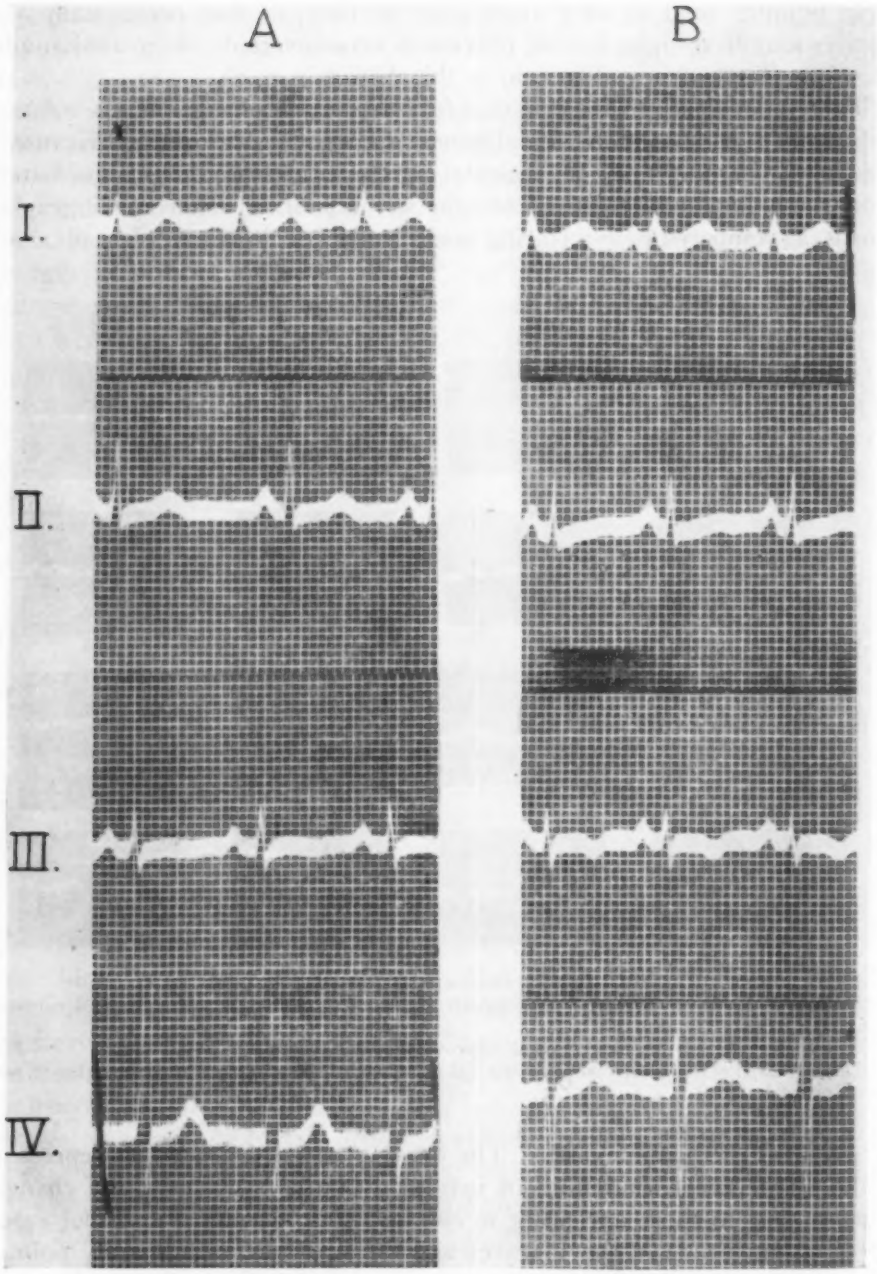

FIG. 5. A. This record was made on an 11-year old girl who was admitted to the hospital for a corrective eye operation. This electrocardiogram was made two days before operation.

B. Record made on the same patient on the operating table, immediately pre-operatively. No pre-operative medication had been given. The child was very apprehensive. Note that T_2 has become almost isoelectric, and T_3 has become definitely inverted. Another record made three days after operation was normal.

mittedly incomplete, of 47 conditions, none of which is due to primary heart disease, but all of which may produce changes in the electrocardiogram similar to those caused by coronary sclerosis and myocardial disease. An appreciation of this fact will make for more rational interpretation of the electrocardiogram and will avoid some of the errors of interpretation that now occur.

Conclusions

1. The electrocardiogram is of great value in the recognition of the cardiac arrhythmias and in the detection of myocardial infarction. It may be useful in determining if and when the heart has become involved during the course of certain systemic diseases, and less frequently, in determining whether or not an individual has been taking certain drugs, notably digitalis.

2. A more widespread recognition of the limitations of electrocardiography is desirable.

3. Little information regarding function of the heart or prognosis can be obtained from the electrocardiogram.

4. The present accepted standards of normality for the electrocardiogram are incorrect, since too many normal healthy young adults show changes which, according to present standards, are diagnostic of heart disease.

Table I

Some Conditions, Not Due to Primary Disease of the Heart, That May Be Associated with Changes in the Electrocardiogram Similar to Those Caused by Coronary Sclerosis and Myocardial Disease

1. *Drugs*
   a. digitalis
   b. quinidine
   c. quinine
   d. atabrine
   e. plasmochin
   f. adrenalin
   g. ergotamine tartrate
   h. atropine
   i. mecholyl
   j. emetine
   k. tobacco smoke (nicotine)
2. *Exercise*
3. *Acute Infections*
   a. pneumonia
   b. trichinosis
   c. diphtheria
   d. typhoid fever
   e. typhus fever
   f. influenza
   g. periarteritis nodosa
   h. undulant fever
   i. pulmonary tuberculosis
4. *Pericarditis*
   a. acute
   b. chronic
5. *Metabolic Disorders*
   a. obesity
   b. hypothyroidism
5. *Metabolic Disorders* Cont'd
   c. hyperthyroidism
   d. artificial fever
   e. acidosis
   f. alkalosis
   g. hypoglycemia
   h. hyperventilation syndrome
   i. serum sickness
   j. thiamin chloride deficiency
   k. nicotinic acid deficiency
   l. acute blood loss
   m. chronic anemias
   n. carbon monoxide poisoning
6. *Renal Disease*
   a. serum potassium retention
   b. serum potassium depletion
   c. acute glomerular nephritis
7. *Acute Upper Abdominal Disease*
   a. acute pancreatitis
   b. uncomplicated gall-bladder disease
   c. bleeding peptic ulcer
   d. perforated peptic ulcer
8. *Pulmonary Embolism*
9. *Autonomic Nervous System Imbalance*
   a. neurocirculatory asthenia
   b. fear

5. The major cause for the more serious mistakes in interpretation is the widespread belief that changes in the QRST complex and especially the ST segments and T-waves are specific for myocardial disease. A list of 47 conditions, not due to primary heart disease, in which similar changes may occur, is presented in proof of the nonspecificity of these changes.

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RENAL CHANGES IN SECONDARY SHOCK*

By PETER A. HERBUT, M.D., *Philadelphia, Pennsylvania*

RECENT medical literature contains numerous contributions on a clinico-pathological entity affecting primarily the kidneys and variously called toxic nephritis (Brown, Eusterman, Hartman and Rowntree [1]), hepato-renal syndrome (Helwig and Schultz [2]), nephrosis (Wilbur [3]), clinically acute nephritis (Bell [4]), acute hematogenous interstitial nephritis (Kimmelstiel [5]), extra renal azotemia (Jeghers and Bakst [6]), acute interstitial nephritis (Melnick [7]), crush syndrome (Bywaters [8]) and so forth. Clinically the syndrome is characterized by either a sudden and obvious onset accompanied by some or all of the manifestations of peripheral vascular collapse, or by a more insidious and imperceptible origin. In either case there is frequently hemoconcentration, a drop in blood pressure, and gradually increasing oliguria ending in anuria and death in uremia. Pathologically the kidneys are usually enlarged, congested, show some obscuring of the corticomedullary demarcations, an eversion of the cut edges and swollen cortices. Microscopically the glomeruli are either normal or congested and contain edema fluid. The tubules are dilated. Their epithelial cells show various degrees of degeneration to complete necrosis and occasionally regeneration and the lumina contain hemoglobin, hyalin or cellular casts. The interstitial tissue is edematous and often infiltrated with plasma cells, lymphocytes and polymorphonuclear leukocytes.

Such a syndrome has been described in a wide variety of clinical disorders some of which are (1) severe infections as peritonitis, septicemia, abscess, pneumonia, etc.,[9, 6, 7] (2) as a result of transfusion reactions,[10, 11, 12, 13] (3) post operatively,[6] (4) intestinal obstruction,[1, 14] (5) crushing injuries,[8, 15] (6) a variety of liver disturbances accompanied or unaccompanied by jaundice,[16, 17, 3, 18, 19] and (7) various unrelated chemicals including the sulfonamides,[20, 21, 32] bichloride of mercury,[2, 22] carbon tetrachloride,[23] iodides,[6] quinine,[24] and cantharidine.[25] Although it is thus apparent that the causes of the syndrome are protean, and that therefore the exact mechanisms involved as expressed by the different authors may also vary, it has perhaps not been generally realized that the one denominator common to many of the cases, regardless of whether the disorder arises abruptly or whether its onset is more insidious, is peripheral vascular collapse or better known as shock.

It is the purpose of this communication to present a group of selected cases representing a wide variety of disease processes that showed the typical clinical and pathological picture of the syndrome as related above, and in which the phenomenon of shock was observed either early in the last

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illness or shortly before death. These cases were selected from approximately the last 1500 necropsies performed at the Jefferson Medical College Hospital covering a period of five years. They represent only a portion of the total number of cases of the syndrome encountered and were selected to show the divergent conditions under which both the syndrome and the phenomenon of shock occur rather than to indicate their frequency.

Case Reports

Case 1. Reaction to Transfusion of Incompatible Blood. A colored woman 36 years old was admitted to the hospital with pneumonia for which she was given a course of sulfonamides for four days. At this time the sulfonamide blood level was 2.3 mg. per 100 c.c. Twelve days after admission she was given by mistake 75 to 100 c.c. of citrated blood of the wrong blood group. There was no immediate reaction but eight hours later her temperature rose to 102° F. and she developed a headache and passed dark brown to black urine. Subsequently she vomited and in a few days developed repeated convulsions. She died in pulmonary edema and severe oliguria seven days after the transfusion. The pertinent laboratory data were as follows: before the transfusion erythrocytes 2,290,000 per cu. mm. and hemoglobin 39.2 per cent whereas the day following the transfusion they were 3,580,000 per cu. mm. and 46.5 per cent respectively: a gradual increase of the blood urea nitrogen and creatinine from normal to 35.2 mg. per 100 c.c. and 6 mg. per 100 c.c. respectively three days before death: following the transfusion persistent high specific gravity, albumin, pus cells, erythrocytes and casts in the urine: a normal fluid intake and output before the transfusion whereas subsequently a fluid intake on successive days of 2275, 2280, 2300, 6000, 5000 and 4600 c.c. with a corresponding urine output of 35,850, none, 30, 75, and 85 c.c.: a normal blood pressure throughout.

Necropsy was performed 11 hours after death. There was no jaundice. The subcutaneous tissue throughout the body contained edema fluid and in addition each pleural and the peritoneal cavity contained 1200 c.c. of clear fluid. The right lung weighed 960 gm. and the left one 800 gm. Each showed marked edema. The spleen weighed 240 gm.; the liver 2000 gm. and each kidney 220 gm. The capsules of the kidneys were slightly adherent to the cortices. Cut surfaces showed congested, swollen cortices, slightly obscured corticomedullary junctions, an eversion of the cut edges and edema of the peripelvic fat and connective tissue.

Microscopically the kidneys showed the changes typical of transfusion reactions. They consisted of relatively normal glomeruli except for congestion and edema of the tufts and often precipitated pink granular material in Bowman's spaces. The proximal convoluted tubules showed marked degeneration of the epithelium with occasional complete necrosis and sloughing, and dilated lumina often filled with precipitated pink staining material. The epithelial cells of the loops of Henle were normally intact but their lumina contained "hemoglobin," erythrocytes, or hyalin casts. Changes in the distal convoluted tubules were the same as those in the proximal ones except that they were less severe and occasionally their lumina contained casts similar to those found in Henle's loops. The interstitial connective tissue disclosed marked edema, engorgement of the capillaries with erythrocytes and scattered lymphocytes, plasma cells and eosinophiles. The collecting tubules showed various types of casts. Microscopic sections of the lungs showed diffuse congestion and edema with early terminal pneumonia. The liver disclosed marked congestion of the sinusoids and edema of the perisinusoidal spaces. There were no other contributory findings.

Case 2. Perforated Cholecystitis and Bile Peritonitis. A white man 55 years old was admitted in a state of prostration with a history of severe epigastric pain and

nausea and vomiting of 24 hours' duration. Operation the following day disclosed a perforated gall-bladder and bile in the peritoneal cavity. The next day he became comatose and remained in this state until death four days later. During his illness the temperature varied between 100° F., and 106° F., and the blood pressure before and after operation between 100 to 140 mm. Hg systolic and 68 to 90 mm. Hg diastolic. During the operation, however, it was 60 to 78 mm. Hg systolic and 50 or not obtainable diastolic for two and one-half consecutive hours. The blood non-protein nitrogen was 70 mg. per 100 c.c. on the day of operation and 150 mg. three days later. The erythrocytes numbered 4,150,000 per cu. mm. the day after operation and 5,600,000 per cu. mm. two days later. On the day of operation and on each subsequent day the fluid intake was 3000 c.c., 2000 c.c., 3000 c.c., 2000 c.c., and 3500 c.c. and the corresponding urinary output was 80 c.c., 100 c.c., 50 c.c., 900 c.c. and 2100 c.c. One recorded urinalysis on admission showed an acid reaction, specific gravity of 1.027 and a cloud of albumin.

Necropsy was performed three hours after death. The peritoneal cavity did not contain bile nor did it show any peritonitis. The gall-bladder was thick, firm, edematous and its tip contained a drain. There was no biliary obstruction and the liver was normal. The left kidney weighed 270 gm. and the right 190 gm. The capsules were adherent and the cortices, dull, rough, reddish brown and irregularly congested. Cut surfaces showed swollen cortices, an eversion of the edges and some obscuring of the corticomedullary demarcations. The perirenal tissue on the right side was indurated, hemorrhagic and showed areas of fat necrosis measuring as much as 5 cm. across. The pancreas was normal. The spleen weighed 350 gm. Permission to examine the thoracic organs was not granted.

Microscopic sections of the kidneys showed the same changes as in Case 1 except that there was more congestion and edema of both the glomeruli and interstitial connective tissue; less degeneration and more dilatation of the convoluted tubules; fewer foci of inflammatory cells, and occasional completely hyalinized glomeruli. The gall-bladder wall was edematous and diffusely infiltrated with plasma cells, lymphocytes and polymorphonuclear leukocytes. Sections of the remaining abdominal organs showed no contributory findings.

Case 3. Ulcerative Esophagitis, Enteritis and Colitis. A white woman 63 years old was admitted with a history of constipation and diarrhea for five years; periodic bouts of nausea and vomiting with poor appetite for three years; belching of gas and hiccoughs for three months and tarry stools for one week. The abdomen became distended 24 hours after admission and with this she became progressively weaker and died 7 days later. The blood pressure was 140 mm. of Hg systolic and 80 mm. of Hg diastolic on admission, but it gradually declined until the day before death it was 80 mm. Hg systolic and 50 mm. diastolic and several hours before death 66 mm. Hg systolic and 44 mm. diastolic. The last erythrocyte count obtained four days before death was 3,000,000 per cu. mm. Previous ones were essentially similar. The non-protein nitrogen level of the blood first taken three days after hospitalization was 286 mg. per 100 c.c. whereas on the day before death it was 192 mg. The daily intake of fluids varied from 2500 c.c. to 3000 c.c. and the corresponding urinary output from 550 c.c. to 1000 c.c. A urinalysis one day before death showed an acid reaction, a specific gravity of 1.011, a cloud of albumin and 10 to 20 pus cells per high power field. The serum van den Bergh was negative.

Necropsy was performed nine hours after death. Each pleural cavity contained an "excess" of serous fluid. The right lung weighed 510 gm. and the left one weighed 410 gm. Cut surfaces of each disclosed congestion and edema. The mucosa of the esophagus, jejunum, cecum and ascending colon contained numerous ulcers that measured as much as 1 cm. across. The mucosa of the jejunum showed in addition a gray pseudomembrane covering the nonulcerated portions. Congestion was

patchy. The right kidney weighed 200 gm. and the left 180 gm. Grossly they were essentially normal. The spleen weighed 90 gm. The remaining organs were normal.

Microscopic sections of the kidneys disclosed marked degeneration of the epithelial cells of the convoluted tubules, especially the proximal ones. Their lumina were markedly dilated and contained pink staining precipitated material and less frequently erythrocytes. Hyalin or "hemoglobin" casts were particularly abundant in the loops of Henle where the epithelial cells were well preserved. They were less frequently present in the distal convoluted tubules. The epithelium of the collecting tubules was undisturbed. Their lumina contained various types of casts. The supporting connective tissue of the cortex showed marked edema, congestion of the capillaries and focal collections of plasma cells and lymphocytes. The glomeruli were congested. Sections of the esophagus, jejunum and colon showed acute nonspecific ulcers with marked congestion of the submucosal capillaries. The lungs disclosed marked congestion and less edema. Sinusoidal congestion and perisinusoidal edema of the liver with compression of the liver cells were severe. Sections of the remaining organs disclosed no contributory findings.

Case 4. Pneumonia. A white man 58 years old was admitted in "an extreme state of cardiac collapse." He was orthopneic, irrational, and examination disclosed bubbling râles in his lungs and trachea, and edema of the ankles. He died one and one-half hours after admission. The erythrocytes numbered 5,000,000 per cu. mm. The hemoglobin was 86 per cent and the white corpuscles numbered 9200 per cu. mm. The blood pressure was 180 mm. Hg systolic and 105 mm. diastolic. The pulse was 130, temperature 102.4° F. and the respirations 50 per minute.

Necropsy was performed 12 hours after death. There were 100 c.c. of fibrinopurulent exudate in the left pleural cavity. The left lung weighed 890 gm. and the right one 480 gm. An acute pneumonic process completely replaced the left upper lobe while throughout the left lower lobe and the entire right lung there was an excess of serosanguineous fluid. The left kidney weighed 230 gm., the right 160 gm., and the spleen 160 gm. Both the kidneys and the spleen were grossly normal.

Microscopically there was severe congestion of the renal glomeruli and interstitial connective tissue. Edema was marked in the latter but only slight in the former. Foci of inflammatory cells were not seen. The epithelial cells of the convoluted tubules were so swollen and granular that the lumina were completely or almost completely occluded. In addition some of the cells were cast off and filled either the same or most distal portions of the tubules. There was no epithelial regeneration. Henle's loops were usually normal, and while the epithelium of the collecting tubules was intact, their lumina contained cellular, hyaline or "hemoglobin" casts. Throughout the liver there were foci of intense congestion and extravasation of blood and plasma. The lungs showed congestion, edema and extensive pneumonia.

Case 5. Intestinal Obstruction and Localized Peritonitis. A colored man, 41 years old, was admitted with severe epigastric pain of one day's duration and nausea and vomiting of a few hours' duration. Six days later he was operated upon for intestinal obstruction at which time a portion of the small bowel was resected. Following the operation dark fluid continued to be extracted through the Wangensteen tube. Five days postoperatively his sclerae became icteric and he died 24 hours later. During the operation the blood pressure was so low that it was not obtainable for 40 consecutive minutes. Subsequently it rose to 98 mm. of Hg systolic and 60 mm. diastolic. A single blood count taken four days after admission showed 5,250,000 erythrocytes per cu. mm.; 106 per cent hemoglobin and 7200 white blood corpuscles per cu. mm. The blood non-protein nitrogen and creatinine rose from normal on admission to 74 mg. and 3.58 mg. per 100 c.c., respectively, two days before death. The daily fluid intake varied from 3000 c.c. to 4000 c.c. and the urinary output from

600 to 1800 c.c. The urine was consistently amber to black and showed a specific gravity of 1.009 to 1.029 and the presence of albumin.

Necropsy disclosed icterus of the skin and mucous membranes. The abdomen was distended and the peritoneal cavity showed both acute localized peritonitis and abscesses. Each kidney weighed approximately 250 gm. The capsules were adherent and the external surfaces were rough and yellowish brown. Cut surfaces showed swollen cortices and everted edges. The right and left lungs weighed 660 gm. and 330 gm. respectively. The spleen weighed 230 gm. and the liver 2080 gm. Both these and the remaining organs were grossly normal.

Microscopically the kidneys showed the same changes as previously described. Degeneration of the proximal convoluted tubules was marked, and their lumina were dilated and filled with pink staining precipitated material. The epithelium of the loops of Henle was uninvolved while that of the distal convoluted tubules showed some degeneration but less than that in the proximal segments. "Hemoglobin," hyaline and cellular casts were prominent in both the loops of Henle and the distal convoluted tubules as well as the collecting tubules. The liver showed congestion of the sinusoids, edema of the perisinusoidal spaces and a diffuse sprinkling with polymorphonuclear leukocytes. The submucosa of the intestine showed marked capillary congestion and edema.

Case 6. Subdiaphragmatic Abscess. A colored man 47 years old was admitted with pain in the upper abdomen, vomiting and weakness of 12 hours' duration. He was restless and his skin was cold, wet and clammy. His temperature was 100° F. and his blood pressure was 60 mm. Hg systolic and 50 mm. diastolic. Although with treatment he reacted satisfactorily, he subsequently had repeated chills, fever and vomiting and died in pulmonary edema 30 days after admission. One day after admission the erythrocytes numbered 5,630,000 per cu. mm. and the hemoglobin was 90 per cent. The next day the erythrocytes numbered 5,200,000 per cu. mm. and the hemoglobin was 86 per cent whereas the remaining counts averaged 3,550,000 per cu. mm. and 77 per cent respectively. Five days before death the blood non-protein nitrogen was 63 mg. per 100 c.c. and the creatinine was 2.7 mg. per 100 c.c. The daily intake of fluids varied between 1840 c.c. and 6000 c.c. while the urinary output varied between 700 c.c. and 3800 c.c. Urinalysis showed a specific gravity about 1.013, albumin 1 + to 3 + and few to many pus corpuscles.

Necropsy performed five hours after death was confined to the abdomen. The peritoneal cavity was normal, but in the left upper quadrant there was a localized subdiaphragmatic abscess containing 100 c.c. of grayish yellow pus and walled off by the spleen, stomach, diaphragm and liver. Each kidney weighed 280 gm. The capsules stripped easily leaving smooth surfaces. Cut surfaces disclosed edema of the cortices and everted edges but were otherwise normal. The spleen weighed 350 gm. and the liver 2450 gm. All the abdominal organs appeared somewhat icteric.

Microscopically the renal changes, as in the cases above, disclosed moderate degeneration of the tubular epithelium; marked tubular dilatation; precipitated granular material in all the tubules; granular casts in the Henle's loops, distal convoluted tubules and collecting tubules and in the latter also hyaline casts; marked congestion and edema of the interstitial connective tissue with foci of lymphocytes and plasma cells, and congestion of the glomeruli. Sections through the abscess wall showed granulation and fibrous tissue infiltrated with a variety of cells of inflammatory origin. There were congestion and edema of the omentum, pancreas and liver and congestion of the spleen.

Case 7. Extensive Burns. A white man, 53 years old, was admitted in a state of severe shock with extensive burns of the face, hands, abdomen and extremities. With treatment he gradually recovered from the acute symptoms and was making satisfactory progress until 32 days after admission when he gradually developed

pulmonary edema, a decline in blood pressure to 50 mm. Hg systolic and 20 mm. diastolic, became stuporous and died two days later. On the day of admission the erythrocytes numbered 6,330,000 per cu. mm. and the following day 5,380,000 per cu. mm., while subsequently they dropped to an average of 3,000,000 per cu. mm. The daily fluid intake varied from 3500 c.c. to 5500 c.c. and the urinary output from 500 c.c. to 4550 c.c. The specific gravity of the urine varied from 1.010 to 1.026 and it consistently showed albumin but was otherwise negative. The non-protein nitrogen was normal until two days before death when the level was 52 mg. per 100 c.c.

Necropsy was performed 14 hours after death. The burned areas of the skin were covered with both crusts and purulent material. There was generalized subcutaneous edema. The left kidney weighed 320 gm. and the right 210 gm. The capsules were not adherent. The cortices were swollen and the cut edges were everted. The left lung weighed 630 gm. and the right 850 gm. Each showed increased crepitations and upon section a marked increase of serosanguineous fluid but no pneumonia. There were severe patchy congestion throughout the intestines and superficial erosions in the duodenum. The spleen weighed 260 gm. and the liver 2050 gm.

Microscopic sections of the kidneys disclosed complete necrosis and swelling of the epithelial cells of the proximal convoluted tubules to such a degree that the lumina were completely occluded. The epithelial cells of Henle's loops were relatively well preserved while those of the distal convoluted tubules showed marked degeneration but were better preserved than those of the proximal convoluted tubules. The collecting tubules contained scattered "hemoglobin" and hyalin casts. The glomeruli were congested. The interstitial tissue showed marked congestion of the lungs, liver and submucosa of the small intestine, and edema of the lungs, liver, corium, and testes.

Case 8. Hodgkin's Disease with Massive Necrosis of Involved Organs. A white man, 49 years old, was known to have Hodgkin's disease for two months during which time he was given deep roentgen-ray therapy. He returned to the hospital with constipation, fever, nausea and vomiting, headache and tired feeling. Deep therapy was continued until death two weeks after admission. Four blood counts disclosed an average of 3,200,000 erythrocytes per cu. mm. and a hemoglobin of 61 per cent. The daily fluid intake varied from 1390 c.c. to 1660 c.c. and the urinary output from 550 c.c. to 750 c.c. The blood pressure readings in mm. of Hg on the following days after admission were: first 80/60; second 80/60; seventh 110/60; eighth 72/50; ninth 80/56; eleventh 70/50; twelfth 60/? and thirteenth 110/70.

Necropsy was performed 17 hours after death. The body was emaciated and jaundiced. Lymph nodes in the left side of the neck, the left inguinal region, mediastinum, along the abdominal aorta and in the left lower quadrant were enlarged to as much as 10 cm. in diameter. They were firm, matted, and on section disclosed yellowish gray tissue. The liver weighed 2540 gm. and the spleen 210 gm. Each contained yellow tumor masses measuring from 1 to 6 cm. across. Each kidney weighed 160 gm. The capsules were not adherent and the external surfaces were dark red and somewhat granular. Cut surfaces were essentially normal. The left lung weighed 510 gm. and the right 610 gm. Excessive frothy serosanguineous fluid was found both within the lungs and in the trachea and bronchi. Microscopic changes in the kidneys were identical with those in the cases already described. Congestion and edema of both the glomeruli and interstitial connective tissue were particularly prominent. Numerous sections taken from the tumor masses described above besides showing a cellular infiltration typical of Hodgkin's disease disclosed massive complete necrosis of approximately three-quarters of the total tumor tissue. Capillo-venous congestion and interstitial edema were particularly conspicuous in the lungs, myocardium and liver.

Case 9. Obstructive Jaundice Caused by Carcinoma of the Pancreas. A white

man, 70 years old, was admitted with pain in the right upper quadrant and jaundice of three weeks' duration. The gall-bladder was large and tender. Three days after admission a cholecystojejunostomy was performed following which the jaundice increased in severity, the urine became almost black and he died in coma on the seventh postoperative day. Before operation the erythrocytes numbered 3,800,000 per cu. mm. and the hemoglobin was 78 per cent; two days after operation they numbered 5,500,000 per cu. mm. and the hemoglobin was 118 per cent; four days after operation the erythrocyte count was 5,000,000 and the hemoglobin 97 per cent. Two days before death the blood urea N was 24.4 mg. per 100 c.c. and the creatinine was 2.25 mg. per 100 c.c. The daily intake of fluids varied between 2360 c.c. and 3360 c.c., and the urinary output varied between 1700 c.c. and 3100 c.c. The urine was brown to black; acid in reaction; specific gravity 1.016 to 1.020; albumin present and many pus corpuscles. The systolic blood pressure varied from 100 to 150 mm. Hg and the diastolic was around 70 mm. Hg.

Necropsy was performed six hours after death. There was extreme jaundice. The head of the pancreas was replaced with a carcinoma 6 cm. in diameter and this partially compressed the common bile duct. The cholecystojejunostomy was patent but contained no bile for the common hepatic duct was by mistake completely ligated. There was much dilatation of the biliary tree above the point of ligation and severe jaundice of the liver. The left kidney weighed 180 gm. and the right 220 gm. Except for being jaundiced they were essentially normal. The spleen weighed 240 gm. Each lung showed increased crepitations and on section marked diffuse congestion and edema, and pneumonia in the dependent portions. The mucosa of the tracheobronchial tree was congested and the lumen contained frothy fluid.

Microscopic changes in the kidneys were similar to those previously described. Capillo-venous congestion and edema of the glomeruli and interstitial tissue were marked. Degeneration of the proximal convoluted tubules was more marked than of the distal ones, but both were dilated. "Hemoglobin" and hyaline casts were present in the lower nephrons. Sections of the pancreas disclosed an adenocarcinoma. In the liver sinusoidal congestion, perisinusoidal edema and precipitated bile pigment were prominent. The lungs disclosed congestion, edema, and terminal pneumonia.

Case 10. Bichloride of Mercury Poisoning. A white man, 50 years old, was admitted to the hospital four hours after he had swallowed five bichloride of mercury tablets. Before admission he had vomited bile and had several bloody bowel movements. Early the following morning he was in a state of shock. His skin was cold, clammy and disclosed beads of perspiration. The pulse could not be obtained; râles developed at both bases of the lungs; dyspnea set in, and he died in pulmonary edema 14 hours after admission. The erythrocytes numbered 5,750,000 per cu. mm. and the hemoglobin was 90 per cent. A few drops of urine obtained by catheter showed 5 to 10 pus cells per high power field but no other abnormalities. The blood non-protein nitrogen was 38.12 mg. per 100 c.c. and the blood pressure was not recorded.

Necropsy was performed four hours after death. There were slight edema of the tibia and cyanosis of the face and fingers. Superficial burns were present in the mouth, lips and tongue whereas in the esophagus, stomach and small intestine there were superficial ulcers and intense congestion of the mucosa. The stomach contained 300 c.c. of thick bloody fluid and the peritoneal cavity about 500 c.c. of watery blood tinged fluid. Each lung weighed 420 gm. and disclosed an excess of frothy fluid. The spleen weighed 240 gm. Each kidney weighed 170 gm. They were brownish red, and from the cut surface there oozed a considerable amount of blood.

Microscopically the kidneys showed complete necrosis and sloughing of the epithelium of the proximal convoluted tubules with complete occlusions of the lumina. The epithelial cells of the lower nephron exhibited only slight degeneration, and the

collecting tubules contained erythrocytes. There was severe congestion of the capillaries of the glomeruli and interstitial connective tissue. Congestion was so marked in the mucosa and submucosa of the esophagus, stomach and intestine as to border on infarction. Congestion and edema of the liver were less intense and more marked in the center of the lobules.

Case 11. Arsphenamine Poisoning. A white woman, 35 years old, received an intravenous injection of 0.3 gm. of arsphenamine and in a few minutes developed hot flashes and dyspnea. Within two hours the dyspnea increased, and there appeared chills, sweats, nausea and vomiting, aching in the extremities and lower spine and cyanosis. Next day icterus appeared and this deepened until she died in coma 10 days after the injection. On admission to the hospital the blood pressure was 90 mm. Hg systolic and 60 mm. diastolic, but on subsequent days rose to as much as 170 mm. Hg systolic and 90 mm. diastolic. The first erythrocyte count and hemoglobin, recorded two days after admission, were 3,100,000 per cu. mm. and 60 per cent respectively, whereas on subsequent examination the erythrocytes numbered as low as 1,650,000 per cu. mm. and the hemoglobin was 35 per cent. In the first 24 hours after injection she excreted only 250 c.c. of mahogany brown urine. The subsequent urine output in 24 hours varied between 200 c.c. and 900 c.c. while the intake of fluids ranged from 2700 c.c. to 4000 c.c. Repeated urinalysis disclosed specific gravity of 1.010 to 1.016, albumin, erythrocytes, pus cells and granular casts. The blood nonprotein nitrogen and creatinine gradually rose to 193 mg. and 10.3 mg. per 100 c.c. respectively.

Necropsy was performed two hours after death. There was jaundice and generalized subcutaneous edema. Each pleural cavity contained 2000 c.c. of blood tinged fluid. The left lung weighed 420 gm. and the right 510 gm. The parenchyma, bronchi and trachea contained a great amount of bloody frothy fluid. Each kidney weighed 415 gm. The external surfaces were smooth and showed scattered petechiae. Cut surfaces revealed swollen cortices, obscured demarcations and considerable congestion. The spleen weighed 240 gm. and the liver 2200 gm. The gall-bladder wall was edematous.

Microscopically the proximal and distal convoluted tubules of the kidney could not be distinguished for all were greatly dilated and lined with greatly flattened and attenuated epithelium. Casts composed of erythrocytes, pus cells, epithelial cells and amorphous material were found in all tubules but were particularly abundant in Henle's loops and collecting tubules. The glomeruli were congested and Bowman's spaces were dilated. The interstitial tissue showed congestion, edema and scattered collections of plasma cells and lymphocytes. The liver cells were degenerated in patchy areas but, throughout, both they and the bile canaliculi contained an abundant amount of bile. The sinusoids were congested. The lungs showed congestion, edema and terminal pneumonia. The bone marrow was active.

Case 12. Diffuse Hepatic Necrosis Caused by Sensitivity to Sulfadiazine. A white woman, 45 years old, was in the hospital one month previously for a hysterectomy at which time she received 4 gm. of sulfadiazine daily for four days. Because she now developed chills, fever and pain in the back she was thought to have pyelitis and so was given a total of 6 gm. of sulfadiazine. Another 3 gm. was administered after she entered the hospital at which time she developed a sharp rise in temperature and a generalized macular rash. The sulfonamide level of the blood at this time was 6.7 mg. Within the next 24 hours she became stuporous, developed twitchings of the facial muscles, then convulsions and jaundice and died in coma two days after the sulfadiazine was discontinued. Before she died 500 c.c. of bloody fluid were aspirated from the stomach and a statement was made that in the last few hours of her life she was "in a state of shock." Two days before death the blood non-protein nitrogen was 62.5 mg. per 100 c.c. and the creatinine 2.11 mg. per 100 c.c.

The urine showed a specific gravity of 1.007 and both albumin and granular casts. The blood pressure was normal and on the day of death the erythrocytes numbered 4,300,000 per cu. mm. and the hemoglobin was 75 per cent.

Necropsy was performed nine hours after death. Each pleural cavity contained 100 c.c. and the peritoneal cavity 1000 c.c. of light brown fluid. Although the right lung weighed only 300 gm. and the left 210 gm. serosanguineous fluid within the parenchyma was in excess of normal and the lumen of the tracheobronchial tree contained frothy fluid. Each kidney weighed 210 gm. The capsules were not adherent. Cut surfaces showed sharp demarcations and swollen, pale, reddish brown cortices. Both pelves and ureters were normal, showing no signs of either hydronephrosis or infection. The liver weighed 1450 gm. It was soft and flabby. Cut surfaces were smooth and dull yellowish brown with numerous dark red hemorrhagic foci in the central portion. The spleen weighed 300 gm.

As in the previous cases the kidneys microscopically showed severe degeneration of the proximal convoluted tubules with only moderate changes in the distal ones. The lumina of the proximal tubules that were patent contained precipitated granular material whereas those of the entire lower nephron contained in addition hyaline and "hemoglobin" casts. There were marked congestion and edema of the glomeruli and interstitial connective tissue and in the latter, foci of plasma cells, lymphocytes and fewer polymorphonuclear leukocytes. Many sections of the liver showed a diffuse and complete necrosis of all the structures with irregular areas of hemorrhage. The lungs disclosed capillo-venous congestion and edema. The spleen was congested in spotty areas.

Comment

The criteria upon which the presence of the phenomena of shock was established in the cases reported here were those set forth by Moon.[26] In some instances the clinical findings were supported by both laboratory and necropsy examination, but when the laboratory data were incomplete, the clinical impression of the attending physician and the findings at autopsy constituted the basis for the diagnosis. More specifically, from the clinical and laboratory standpoints, case 1 developed a delayed reaction following a transfusion with a hemoconcentration of 1,290,000 erythrocytes per cu. mm. or 56 per cent of her normal, and finally died in pulmonary edema. Case 2 was admitted in prostration and for two and one-half consecutive hours during operation the blood pressure ranged from 68 to 90 mm. Hg systolic and 50 mm. Hg or not obtainable diastolic. Two days after operation there was a hemoconcentration of 1,450,000 erythrocytes per cu. mm. or 35 per cent, but because there was no record of an erythrocyte count before operation this, if anything, is a low estimate. In case 3 both the clinical and laboratory data were inconclusive, but the pathologic findings were typical of shock and will be considered below. Case 4 died before studies could be completed. It was stated, however, that he was admitted in an "extreme state of cardiac collapse" and pulmonary edema. His erythrocytes numbered 5,000,000 per cu. mm. and this probably represented a hemoconcentration. In case 5 for 40 consecutive minutes during the operation the blood pressure was so low that it could not be obtained. Only one blood count was recorded and it undoubtedly showed hemoconcentration for the erythrocytes numbered 5,250,000 per cu. mm. and the hemoglobin was 106

per cent. A third indication of shock was the extraction by way of the Wangensteen tube of darkly colored gastric fluid that was presumably partially digested blood. Case 6 on admission showed all the classic signs and symptoms of shock. The blood pressure was 60 mm. Hg systolic and 50 mm. diastolic and the first blood count taken 24 hours after admission disclosed 5,630,000 erythrocytes per cu. mm. If subsequent counts of 3,550,000 erythrocytes per cu. mm. could be taken as his normal there was a hemoconcentration of 2,080,000 or about 60 per cent. He died in pulmonary edema. Case 7 was admitted in shock with an erythrocyte count of 6,330,000 per cu. mm. Although his normal count was not known, there is nevertheless little doubt that this represented a hemoconcentration of at least 50 per cent. For two days before death his blood pressure was around 50 mm. Hg systolic and 20 mm. diastolic and he died in pulmonary edema. The only clinical manifestation of shock in case 8 was perhaps a blood pressure of 60 to 80 mm. of Hg systolic and not obtainable to 60 mm. of Hg diastolic for two weeks prior to death. In case 9 there was a postoperative hemoconcentration of 1,700,000 erythrocytes per cu. mm. or 44 per cent and an increase of hemoglobin from 78 per cent to 118 per cent. Case 10 besides showing the classic signs and symptoms of shock showed an erythrocyte count of 5,750,000 per cu. mm. which, because he was passing blood both in the stool and in the vomitus, represented a considerable hemoconcentration. The presence of the phenomenon of shock in case 11 was based upon the history of a reaction with a decline in blood pressure to 90 mm. Hg systolic and 60 mm. diastolic. Little can be said about hemoconcentration because an erythrocyte count was not done immediately. Finally, in case 12 the clinical data indicating shock were the history of a reaction, 500 c.c. of bloody fluid withdrawn from the stomach and the statement that preceding death the patient was in "a state of shock."

Both in experimental and clinical shock Moon [26] has described highly characteristic and constantly occurring pathologic changes. Fundamentally they consist of capillary atony due to injury of the endothelium, and are represented by dilated and engorged capillaries with extravasation of edema fluid and even erythrocytes into the adjoining parenchyma. While this change is almost always observed in the lungs it is also found fairly consistently in the liver, kidneys, gastrointestinal tract and other tissues. In addition, there is often an accumulation of serous or blood tinged fluid in the body cavities, frothy fluid in the tracheobronchial tree, terminal pneumonia, "coffee-ground material" in the stomach, and blood tinged mucus in the rest of the gastrointestinal tract. Although all the cases reported here showed various combinations of the above mentioned pathological changes, those most constantly observed were congestion and edema of the lungs, liver and kidneys and terminal pneumonia. Of special interest, perhaps, were the sinusoidal congestion and perisinusoidal edema so constantly seen in the liver, for these are in fact the changes seen in so-called serous hepatitis.

The morphologic changes in the kidneys in delayed lethal cases of acute

or incipient shock are so characteristic that a diagnosis can be highly suspected grossly and be made at a glance microscopically. The kidneys are usually enlarged. The capsules may or may not be adherent and the cortices are either smooth or granular. Cut surfaces show congestion, swollen cortices, an eversion of the edges, and sometimes obscured demarcations. Histologically the most striking changes are congestion and usually marked edema of the interstitial connective tissue with or without an infiltration of plasma cells, lymphocytes and less frequently polymorphonuclear leukocytes. There is severe degeneration to complete necrosis and even regeneration of the epithelial cells of the proximal convoluted tubules with relatively less degeneration of the distal convoluted tubules and still less or none at all of the lining cells of Henle's loops and the collecting tubules. Granular pink staining material is found in the proximal convoluted tubules and hyaline, "hemoglobin" or epithelial casts are present in the loops of Henle, the distal convoluted tubules and the collecting tubules. The glomeruli are usually congested and Bowman's spaces frequently contain edema fluid. Other renal changes that may be found are incidental.

Because of the widely divergent clinical conditions under which the renal changes as described can occur, it is quite evident that there is no single causative agent of the syndrome. Although certain substances, as for example bichloride of mercury,[28] are known to act directly upon the tubular cells of the kidney, they also cause destruction of other body tissues as for instance the mucosa of the intestines. It is highly probable that other chemicals may act solely by destroying body tissues with the liberation of protein or protein split products and that these in turn act upon the kidneys. One can in fact go a step further and say that any tissue poison be it a chemical, bacterium, toxin or trauma, which will cause tissue destruction with liberation of proteins or protein split products will thus indirectly produce the renal changes described above. These injurious agents may act either directly upon the tissues or indirectly by damaging the capillary endothelium and producing tissue anoxia. This is not a new concept for Hewitt [9] in 1906 quotes Orth as saying that necrosis of the epithelium of the tubules can be produced by anemia of the tissues from various causes. Cooke and Whipple [27] in 1918 demonstrated in animals that a general toxic reaction with a rise in blood non-protein nitrogen is due not so much to the chemical agent or the bacteria as such, as it is to local cell injury or necrosis with the escape of toxic protein split products. Also experimentally Moon [26] has shown that one of the best methods of producing shock in dogs is the parenteral administration of ground tissues. This fact needs no better clinical support than the many excellent examples of shock and renal damage, as reported by Bywaters,[8] that developed in patients with crushing injuries. Of the present series of cases the two best examples of production of the syndrome by tissue destruction are case 8 in which approximately three-fourths of the tumor tissue was completely necrotic, and case 12 in which there was complete necrosis of the liver.

Whereas in some cases functional renal changes are not striking, in others they are characteristic and consist of anuria or oliguria with often a highly colored urine, relatively high specific gravity, albumin, casts, erythrocytes and pus cells. These are accompanied by retention of nitrogenous waste products in the blood stream. The mechanisms responsible for these changes are undoubtedly many and rather complex. Jeghers and Bakst [6] in their excellent article on extrarenal azotemia listed the causes of the syndrome under the following six headings: (1) a drop in blood pressure below the patient's normal, for it has been shown that as the systolic pressure drops the volume of urine decreases until a systolic pressure of 70 mm. Hg is reached when urine formation ceases entirely, (2) hypochloremia because of the concomitant loss of fluid and hyponatremia which produce a diminished blood plasma volume, (3) dehydration (which is accompanied by hemoconcentration), (4) liver damage with failure to synthesize the amino acids, (5) increased protein catabolism and (6) local renal disturbances consisting of changes in reabsorption activity of the tubules; control of the blood supply by afferent and efferent arterioles; stimulation of splanchnic nerves producing a decrease in the amount of urine secreted; rise in urine pressure in the intracapsular and tubular spaces due to blockage of the tubules; edema of the kidney substance producing an increase in the urine pressure, and hormonal control of renal function.

Although the above mentioned items appear to cover all the factors responsible for the functional derangement of the kidneys, there are a few points that need emphasis. The first is concerning the altered function of tubules when their epithelial cells are destroyed. In 1929 Richards [28] showed that by inhibiting the action of the tubular epithelium with mercury bichloride there was no urine secreted into the ureter and yet by actual measurement the glomerular filtrate was increased. His explanation was that the osmotic pressure of the blood proteins is unobstructed by the normal qualities of the tubular epithelium and is able to draw most of the glomerular filtrate back into the blood stream. If this is so when the blood is normal then it should be doubly so when there is hemoconcentration as is usually the case in shock.

Secondly, emphasis should be placed upon the interference with normal glomerular dynamics. In the normal human kidney Smith et al.[29] have shown that the effective glomerular pressure is the difference between the hydrostatic pressure in the efferent end of the glomerular capillary and such pressure distally as may oppose this pressure. The opposing pressure consists of (1) renal venous pressure which is normally negligible, (2) renal interstitial pressure and (3) the osmotic pressure of the blood. In shock there is (1) venous stagnation,[30, 31] (2) an increase in the renal interstitial pressure due to edema and (3) hemoconcentration with an increase in the osmotic pressure of the blood. The net result is a total increase of the opposing pressure which with an already decreased head force [31] due to a decline in the blood pressure reduces greatly the effective glomerular filtra-

tion, and this in turn diminishes the volume of urine secreted. This results in a retention of nitrogenous waste products in the blood stream.

Thirdly, it should be emphasized that the effective glomerular filtration pressure is further reduced in these cases of shock by an actual mechanical obstruction of the tubules, with an increase of tubular and capsular urine pressure. Tubular obstruction is accomplished by the formation of hyaline casts filling completely the lumina of the loops of Henle or of the more distally located tubules and the terrific swelling of the epithelial cells of particularly the proximal convoluted tubules. Tubular obstruction is manifested morphologically by (1) dilatation of the proximal convoluted tubules and Bowman's spaces sometimes to a marked degree, and (2) the accumulation of precipitated pink staining granular material in the same locations.

It is the rule rather than the exception that in this syndrome the specific gravity of the urine is relatively high in spite of the apparent renal insufficiency. This can be accounted for by the morphological changes in the kidneys. The glomeruli are almost always intact, and so the glomerular filtrate although reduced as a result of altered glomerular dynamics, might still be of sufficient quantity to carry on the excretion of waste products if the tubular epithelium were intact, but since in all cases this shows degeneration to complete necrosis most of the filtrate is withdrawn back into the blood stream.[28] That which is left is further concentrated by the loops of Henle whose normal function it is to concentrate the urine and whose epithelial cells, in the cases presented here, were always relatively intact. That their function is unimpaired is supported by the fact that hyaline casts were found only in the loops of Henle and beyond—at the location where the water was removed and the protein sufficiently concentrated, and never in the proximal convoluted tubules where the filtrate was more dilute.

Summary

Twelve cases of delayed death following acute or incipient shock produced by (1) a reaction to transfusion of incompatible blood, (2) perforated cholecystitis and bile peritonitis, (3) ulcerative esophagitis, enteritis and colitis, (4) pneumonia, (5) intestinal obstruction, (6) subdiaphragmatic abscess, (7) burns, (8) Hodgkin's disease with tissue necrosis, (9) obstructive jaundice, (10) bichloride of mercury poisoning, (11) neoarsphenamine poisoning and (12) diffuse hepatic necrosis caused by sulfadiazine are presented. Clinically there were varying degrees of oliguria, high specific gravity of the urine with albumin, casts, erythrocytes and pus cells, and a retention of non-protein nitrogen in the blood.

The pathologic changes in the kidneys are quite characteristic, and in the literature they have been described under a variety of names. Grossly the kidneys are enlarged and the capsules strip easily leaving smooth or finely granular surfaces. Cut surfaces show congested swollen cortices, an eversion of the edges, and sharp or slightly obscured corticomedullary demarca-

tions. Microscopically there are (1) congestion and edema of the interstitial connective tissue with or without cellular infiltration, (2) severe degeneration to complete necrosis of the epithelium of the proximal convoluted tubules with less degeneration of the distal convoluted tubules and still less or none at all of the lining cells of Henle's loops and collecting tubules, (3) granular pink staining material in the proximal tubules and various types of casts in the distal nephrons and (4) congestion and edema of the glomeruli.

Although the ultimate causes of the renal changes are divergent one denominator common to many of the cases is shock and, therefore, these changes are regarded as characteristic of this phenomenon.

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ACUTE MEDIASTINAL EMPHYSEMA *

By BERNARD M. SCHWARTZ, Captain, M.C., *New York, N. Y.*, GEORGE H. MCILROY, Captain, M.C., *Cincinnati, Ohio,* and HARRY A. WARREN, Lt. Colonel, M.C., F.A.C.P., *Peoria, Illinois*

THE syndrome of acute mediastinal emphysema following trauma or pulmonary disease has been recognized for many years, but it is only recently that Hamman [1, 2] has called attention to the spontaneous occurrence of this condition. Numerous case reports [3-18] have been published following his description, but it is still regarded as a rare entity. Recently, moreover, reports of mediastinal emphysema secondary to other conditions have been less common than those of the spontaneous type. This subject is particularly important at the present time because many cases following trauma [19] and influenzal pneumonia [20, 21, 22] were reported during World War I and undoubtedly more cases have occurred during the present conflict. Cases in the United States Navy,[18] United States Army,[23] and the Royal Canadian Air Force [14] have already been reported. One of these occurred in an aviator who bailed out of an aeroplane after a mid-air collision [18] and another in a soldier exposed to chlorine gas.[23] Lovelace and Hinshaw [24] have stressed the care with which all patients with chest injuries must be examined for signs of pneumothorax and mediastinal emphysema before embarking on aerial flights, in view of the marked increase in the pressure of air in closed cavities at high altitudes. We are reporting seven cases of mediastinal emphysema occurring in soldiers at an Army Air Force Technical School. One case was associated with an acute respiratory infection and bronchial asthma and subsequently developed an atypical pneumonia, while six were of the spontaneous type. Two of these cases are of special interest in that they ran a prolonged course, differing from the usual description of this syndrome.

Mediastinal emphysema has been described in association with many conditions. It occurs following trauma to the chest, either penetrating or non-penetrating, and with or without tension pneumothorax.[19, 25] It has been reported following surgical procedures on the neck [26] and the thorax; following positive pressure anesthesia [27]; after therapeutic pneumothorax [28] or traumatic or therapeutic pneumoperitoneum.[29] It occurs in association with acute infections, such as pneumonia,[20, 21, 22, 30] influenza,[31] diphtheria, and whooping cough, or severe coughing spells. It may occur with severe bronchial asthma [32, 33] or tuberculosis,[34] or after exposure to pulmonary irritants.[23] It has been reported during labor and straining at stool, and it may occur in the newborn.[37, 41] The clinical picture produced in association with these conditions differs not essentially from that arising spontaneously

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From the Medical Service, Regional Hospital, Truax Field, Wisconsin.

except that fatal cases have invariably occurred in the secondary group, and in this group clinical symptoms are apt to be more severe.

Pneumothorax occurs in many of these cases. It is usually small, occurring at either apex, more commonly on the left.[2] Unilateral or bilateral tension pneumothorax may result, however, especially in infants. The association of pneumothorax with mediastinal emphysema is so frequent that the presence of air in the mediastinum must be considered in all cases of pneumothorax. Hamman, especially, has pointed out this association and has suggested that the etiology of spontaneous pneumothorax may be mediastinal emphysema in a considerable proportion of cases.[43]

Mode of Production

The possible mechanisms of production of mediastinal emphysema, with or without pneumothorax, may be summarized as follows. The primary source of the air in most cases is a ruptured alveolus or alveoli within the lung. Hamman [2] believes this is the mechanism in "spontaneous" cases. It may occur in normal lungs by extreme over-inflation, as has been demonstrated experimentally by Macklin,[38] Joannides and Tsoulos,[39] and Kelman,[22] and as has presumably occurred clinically in those cases induced by positive pressure anesthesia,[27] those occurring in the second stage of labor,[35] and in some after tracheotomy.[26] It may occur in pathological lungs with weakened and distended alveolar walls, as has been observed following influenzal bronchopneumonia,[20, 21] bronchial asthma [32, 33] and congenital atelectasis.[36] Macklin [38] and Biering [36] have called attention to the importance of areas of atelectasis which stretch the surrounding alveoli and may cause easy rupture of the stretched alveolar membranes, allowing air access to the interstitial tissues. From the area of these ruptures, air may spread in two directions. It may spread to the periphery of the lung [20, 21, 40] and form emphysematous blebs which may rupture and produce a pneumothorax; or subpleural air may dissect back to the pulmonary hilus and then into the mediastinum. Macklin [38] has shown experimentally that air from a ruptured alveolus can also move along the perivascular sheaths in the lung to the mediastinum and extend between the parietal pleura and pericardium.

From the mediastinum the air may spread in several directions. It may rupture the thin mediastinal pleura and produce a pneumothorax. Macklin has demonstrated that this method occurs in cats experimentally and it is probable that this is the mode of production of pneumothorax in the spontaneous cases. The air may also spread upward producing a subcutaneous emphysema of the neck,[2] even extending to the face [33] and downward over the chest wall. This is not an infrequent occurrence and is of course definite proof of the diagnosis of mediastinal emphysema. Air in the mediastinum has also been reported to dissect downward to the retroperitoneal tissues and even to the scrotum and perirectal tissues.[16]

There are other methods for the access of air to the mediastinum but

these are associated with trauma or surgical procedures. Air may be sucked directly into the mediastinum through wounds, such as those due to abdominal injuries or wounds of the neck. Wounds of the trachea or bronchi may also allow access of air to the mediastinum.[25]

Macklin [38] feels that enough pressure can be produced by the air on the pulmonary vessels and pulmonary hilus to cause embarrassment to the circulation. Others have demonstrated collapse of the pulmonic and systemic veins.[25] Apparently, in the spontaneous cases reported thus far, the pressure of air in the mediastinum has not reached sufficient magnitude to produce circulatory obstruction, or else extension of the air to other tissues has relieved the pressure. In this connection, Torrey and Grosh [21] observed marked relief of circulatory and respiratory embarrassment when subcutaneous emphysema appeared in their cases of influenzal pneumonia with pulmonary and mediastinal emphysema.

Clinical Picture

There are two outstanding features in the clinical picture of acute mediastinal emphysema: pain in the chest and a characteristic sound synchronous with the heart beat, described as crunching, bubbling, or clicking.[12] The pain is usually noted first in the left upper or midchest. It then becomes substernal and may radiate to the back, shoulder or arm, particularly the left arm. In many respects it closely simulates the pain of angina pectoris.[8] It may be a severe, sharp, even agonizing pain. It is aggravated by motion, walking or movements of the trunk, and is somewhat relieved by rest. It is made worse by respiration and in this respect simulates acute pleurisy or acute pleurodynia. It may produce a guarded shallow type of breathing. After a variable period, in one of our cases approximately one hour, the patient may become aware of a crunching sound and sensation over the heart, more marked while leaning forward or lying on the left side. The pain may be aggravated by swallowing or turning the head. It usually subsides within a few hours and the patient is then quite comfortable, particularly if he remains quiet. The patient may prefer the recumbent position [5] or a hunched over sitting position, as in two of our cases. Hyperesthesia of the skin over the precordium may be present.[12]

On physical examination the bizarre sounds heard over the precordium are diagnostic. They are caused by the heart contracting against bubbles of air lying between the parietal pericardium and the parietal pleura or within the mediastinal tissues or the lung. These sounds are difficult to describe accurately. Various adjectives have been used, any one or all of which may be applicable in any case. They may be described as clicking, crackling, crunching, creaking, bubbling, crushing, or popping. Cowart [18] has compared them to the "sticky, popping sounds of noisily chewed gum." They are occasionally mistaken for a pericardial or pleuro-pericardial friction rub. They vary with respiration and may be completely obliterated in various

phases of the respiratory cycle. They vary also with the position of the patient, being most frequently audible with the patient lying on the left side. They may disappear on standing erect. After several hours they may disappear entirely but usually can be brought out again by mild exercise, such as sitting up in bed. The sounds may be heard over the whole precordium, or they may be localized to the region of the apex or to the midsternum. In one of our cases they disappeared from the apex but could still be heard over the upper sternum. The patient is usually aware of the sounds, not only feeling their vibrations but occasionally actually hearing the clicking as well. One patient described this sensation "as if gears were grinding together" in his chest.[15] He even may feel them on swallowing.[10] Occasionally they may be heard at a considerable distance from the patient. Frequently the sounds are palpable and have a short inconstant clicking sensation as distinct from the purr of a palpable vascular thrill. A phonocardiogram recorded in one case by Hoffman, Pobirs, and Merliss [17] revealed the sounds to be synchronous with the cardiac impulse and occurring regularly with each cardiac contraction.

On percussion there may be no obvious change, but not infrequently there is diminution of cardiac dullness and even actual hyperresonance substernally or over the heart. The magnitude of this change of course depends upon the amount and position of the mediastinal air. Within 24 hours, occasionally sooner, a subcutaneous emphysema may appear in the tissues of the neck. When present, this confirms the diagnosis.

When first seen the patient may be in mild shock due to the severity of the pain. In the spontaneous cases, however, this is usually not marked and is relieved by rest and sedation. There is usually no associated change in the pulse or blood pressure, no elevation of temperature, and no sign of venous obstruction. In the secondary type this may not be true, and the accumulation of air may be great enough to cause circulatory embarrassment with a picture similar to cardiac tamponade.

Careful physical examination of the chest may give the signs of a pneumothorax, but usually this is so small that it is not evident on examination.

Roentgen-ray examination of the chest may confirm the diagnosis.[2, 4, 12, 41] Frequently there will be a thin line parallel to the cardiac border on either side or in only part of its extent, with an area of increased radiolucency between it and the heart. This line is due to air dissecting between the parietal pericardium and pleura and disappears with the absorption of the air. On oblique or lateral views small or large collections of air may be seen in the mediastinum. A helpful confirmatory finding is the frequent presence of a small pneumothorax, usually over the apex of the left lung. This also may be seen best in an oblique view. Occasionally a small pleural effusion may accompany the pneumothorax, as in our case 2.

Electrocardiograms show no distinctive changes. The white blood count may be moderately elevated but is usually normal. Sedimentation rates are within normal limits.

Differential Diagnosis

Difficulties in differential diagnosis should not be encountered in typical cases, once one is familiar with the bizarre sounds which occur over the precordium in this condition. There are two diseases most commonly confused with this picture—acute pericarditis and acute coronary occlusion with myocardial infarction. Acute pericarditis can be differentiated by the lack of fever and leukocytosis and the absence of electrocardiographic signs. The crunching, clicking sounds over the heart do not have the typical to-and-fro sound of a friction rub and once heard will not be confused with it. Acute coronary occlusion must be considered with the distribution of the pain. There are several factors, however, which are not found in coronary occlusion. The pain in coronary occlusion is not especially affected by respiration as it is in mediastinal emphysema. No sounds occur over the heart in coronary occlusion as occur in mediastinal emphysema. Fever, increased sedimentation rate, leukocytosis and electrocardiographic changes will finally serve to differentiate the two conditions. It must be remembered, however, that rarely there may be absence of pain or of the characteristic sounds. The patient may even walk about asymptomatic.

Greene [13] has described knocking and tapping sounds over the heart in patients with a left pneumothorax. He did not hear the crunching, bubbling sounds typical of mediastinal emphysema, however, unless it was also present. He concluded that the "bubbling, crunching, clicking, and some of the tapping sounds" are due to the heart rubbing against emphysematous blebs in the lung and mediastinum. The knocking and tapping metallic sounds occurred only with a left pneumothorax with the heart striking a bleb over a partially collapsed lung or striking the diaphragm over a gas bubble in the splenic flexure of the colon. Our fifth patient presented both types of sounds over the precordium, and in this case the left pneumothorax was the largest in our group. Similar metallic sounds were heard by Smith [42] and others in soldiers with wounds of the left chest in World War I. Unless one examines the patient in different positions to elicit the characteristic sounds, one may overlook them and miss the diagnosis completely or attribute all symptoms erroneously to the small associated pneumothorax. Hamman [43] has suggested that the etiology of spontaneous pneumothorax may be mediastinal emphysema in more cases than is usually considered.

Treatment

The treatment consists of bed rest. The patient usually is comfortable after resting a few hours, although analgesics or sedatives may be necessary. There is a definite tendency to recurrence. This has been noted among cases reported in the literature, and we noted it in five of our cases. We feel the patient should be kept at bed rest for several weeks until absorption of the air is complete and then allowed gradual return to full activity. In the

secondary cases with the symptoms of mediastinal obstruction with cyanosis, weak pulse, and dyspnea, it is possible that surgical incision in the suprasternal notch would be necessary for evacuation of air and relief of pressure.[44] Incisions over the skin of the chest wall and direct aspiration of air with a needle have afforded relief from marked subcutaneous emphysema.[88]

Acute cellulitis of the mediastinum as a result of mediastinal emphysema has not been reported, but it would appear to be a potential complication, particularly if there is an associated respiratory infection. In several of our cases we used sulfadiazine in small doses as a prophylactic measure. We feel that if respiratory infection is present, prophylactic chemotherapy is advisable to reduce the possibility of a dangerous mediastinal infection.

Case Reports

Case 1. A 19 year old white male soldier was admitted on September 4, 1943, complaining of difficulty in breathing and a sore throat which was aggravated by successive bouts of coughing. The patient had begun to suffer from his annual attack of hay fever approximately three weeks prior to admission. Cough started on September 1, becoming productive of clear mucoid sputum within two days. On the day of admission his throat had become so sore and painful that he could no longer swallow food. Pain in the chest substernally, accentuated by coughing, first appeared on the evening of hospital admission and radiated upward into the neck anteriorly and bilaterally. There was no history of trauma or of sudden sharp pain in the chest. Physical examination on admission showed moderate nasal obstruction. There was exudate and marked diffuse injection of the posterior pharynx. There was extensive crepitation of air beneath the palpating fingers as well as exquisite tenderness in the supraclavicular areas and in the subcutaneous tissues of the neck bilaterally. There was a funnel-shaped depression of the sternum above the xiphoid cartilage. The respirations were labored and difficult. Percussion over the superior mediastinum yielded a tympanitic note and felt "spongy" to the palpating hand. Wheezes and râles of the asthmatic type were prominent over both lung fields, and tactile fremitus was generally increased.

Temperature was 99.6° F., pulse 90, respirations 22, blood pressure 124 mm. Hg systolic and 80 mm. diastolic. Laboratory data on admission were as follows: erythrocyte count 4,820,000 per cu. mm.; leukocyte count 9,450 per cu. mm.; hemoglobin 80 per cent; differential count normal. The urine was normal. Electrocardiogram was within normal limits. Roentgen-ray examination of the chest was normal on admission, but on the fifth hospital day revealed a small patch of pneumonia adjacent to the right heart border about 4 cm. in diameter and of a lobular distribution. No radiological evidence of pneumothorax was found. The heart shadow was not unusual. Subsequent films on the eleventh day showed migration of the lobular pneumonia to two new areas, one in the periphery of the right lower lobe and one in the right middle lobe. On the eighteenth day roentgen-ray examination showed regression of all three patches of pneumonia with parenchymal residua still present. The final examination one week later showed the lungs to be clear. The blood and urine examinations were repeated and found unchanged. Electrocardiogram on the twenty-first day showed no significant changes. Sputum showed no acid-fast bacilli throughout the hospital stay and no predominant organisms as a cause of the pneumonia. The subcutaneous crepitation gradually disappeared by the end of the first week at bed rest, though he continued to have slight pain in the right chest. He was dismissed after one month in the hospital with no positive findings remaining.

Comment. In this case, there were two factors which favored the development of interstitial pulmonary emphysema, the asthma and the acute respiratory infection. Possibly an early pneumonia, not demonstrable on the first roentgenogram, also was a contributing etiological factor. It is quite probable that the infection weakened the alveolar walls and the paroxysms of coughing and the asthma brought about the rupture of an alveolus.

Very probably, the patient's sore throat and difficulty in swallowing were as much related to the emphysema of the tissues as to the local infection in the throat. We classify this case as one secondary to respiratory infection and bronchial asthma.

Case 2. A 22 year old white male soldier was first admitted to the hospital on October 10, 1943 complaining of intermittent, sharp stabbing pain in the left anterior chest. Aside from a slight "head cold" without marked cough, of three weeks' duration, he was well until approximately 48 hours before admission when, while sitting still, he experienced a sharp stabbing pain in the precordium which radiated to the left shoulder and elbow and through to the back. The pain continued with variable intensity, was intensified by deep inspiration, and abated on bed rest.

The patient was well developed and well nourished and appeared to be in no acute distress at the time of admission. His temperature was 101.2° F., respirations 26 per minute, pulse 110 per minute, blood pressure 130 mm. Hg systolic and 90 mm. diastolic. The pharynx was slightly injected with a small patch of white exudate in the left tonsillar fossa. The lungs were clear on auscultation and percussion. The heart was not enlarged to percussion or palpation, there was a "palpable snap" in the third and fourth left intercostal spaces parasternally. The heart sounds were of good quality. The rhythm was regular. Loud "popping, scratching" sounds were heard in the third and fourth interspaces in both systole and diastole.

Leukocyte count on admission was 16,700 per cu. mm., five days later was 12,200 with 64 per cent polymorphonuclear leukocytes, and thereafter was normal. Sedimentation rates were normal. Throat culture revealed a non-hemolytic streptococcus. Several electrocardiograms at intervals of three to four days were within normal limits. Roentgenogram of the chest on admission showed a small left apical pneumothorax and slight clouding of the left costophrenic angle. Eight days later the air had been reabsorbed, but one week after that a small left pneumothorax, both apical and lateral, was again seen, along with a small amount of fluid in the left costophrenic angle. The pneumothorax did not again disappear until the twenty-seventh hospital day.

The temperature rose to 101.2° F. the day after admission, but he was afebrile for the remainder of his hospital stay. On bed rest the patient felt comfortable, but the peculiar precordial sounds continued to be heard for four weeks. During this time they frequently could be heard in the left lateral position. Occasionally they could be heard with the naked ear while standing at the bedside.

After 71 days, he was discharged home on a convalescent furlough for 15 days, but on January 7 had to be readmitted to the hospital because of a recurrence of sharp pain in the precordium with radiation to the back and left lateral chest wall. He stated that the pain had reappeared shortly after discharge from the hospital and had confined him to bed during most of his furlough. He had slight exertional dyspnea during this time. On admission physical examination was negative, as were further leukocyte counts, sedimentation rates, electrocardiograms, and roentgenograms of the chest. On the fourteenth hospital day, however, transient "scratchy" sounds, of the

same character as heard previously but of less intensity, were again heard. On the sixteenth day they were bubbly and popping and heard intermittently until patient's transfer to an Army General Hospital on January 28.

Except for the initial examination at the Army General Hospital, when a few "scratching to-and-fro" sounds were heard over the heart, no abnormal physical or laboratory findings were found. He was again discharged to duty on February 22 with a recommendation for light duty, not requiring strenuous physical exertion.

On March 7 he was again admitted complaining of left anterior and substernal chest pain of variable intensity, most marked on exertion. While in the hospital at bed rest the same characteristic sounds were heard transiently over the heart. These finally subsided again and the patient was discharged to duty on April 19.

Comment. At the outset, the patient presented the classic features of spontaneous mediastinal emphysema (except that his temperature and white blood cell count were elevated due to a mild upper respiratory infection), and it was expected that his convalescence would follow the same smooth course that all previously reported cases seemed to run. Despite four prolonged hospitalizations, however, the patient continued to complain of aches in the chest, and intermittently a few signs were heard over the heart which would seem to substantiate the fact that he was continuing to have mediastinal emphysema. It is possible that the process was in the nature of a "slow leak" rather than a repeated series of new accidents. At the present time, he is on limited duty.

Case 3. A 23 year old white male soldier was admitted May 5, 1944 complaining of severe pain in the left anterior chest. The past history and family history were non-contributory. He had had a mild respiratory infection with cough for two weeks. Suddenly, while walking, he had severe pain in the left anterior chest with numbness and pain in the left shoulder. The pain was accentuated by respiration. On examination he was perspiring, appeared frightened, and had difficulty breathing because of pain. Over the precordium were crackling, snapping sounds synchronous with the heart beat but varying with respiration and louder while lying on the left side. There was a palpable rub over the cardiac apex synchronous with the sounds. Percussion dullness was diminished over the sternum. Pulse was 68, blood pressure 120 mm. Hg systolic and 70 mm. diastolic. Laboratory examinations showed a normal leukocyte count, sedimentation rate, and urine. The temperature was 99° F. on admission and remained normal during his stay in the hospital. Roentgen-ray examination of the chest on admission showed a small left apical pneumothorax. Three days later roentgen-ray examination again showed the pneumothorax and a small linear area of emphysema along the left heart border. After 18 days the pneumothorax and emphysema were completely reabsorbed. He quickly obtained relief with 0.030 gm. of codeine sulfate and bed rest and had no more discomfort. The precordial sounds were audible in diminishing intensity for seven days. He was kept at bed rest for three weeks and then allowed up for light activity. On the thirtieth hospital day while sitting in the barber's chair he suddenly had left chest pain which was again associated with pain and numbness in the left shoulder. On resting the pain became less, but on walking it quickly became much worse. About one hour after the onset of the pain he noticed the crackling sensations over his heart. Examination showed the same findings as on admission. The precordial sounds were audible for four days and then disappeared. Roentgen-ray examination did not show a pneumothorax but did show a linear area of emphysema along the left heart border. Electrocardiograms showed no abnormalities in the limb leads. In the precordial leads V_1 showed an in-

verted T-wave and V_2 a diphasic T-wave. V_5 was of low amplitude. Four days later the precordial curves showed all T-waves upright and of greater amplitude.

Comment. This is a classical example of spontaneous mediastinal emphysema with recurrence. It is interesting in the history of the recurrence that the pain in the chest appeared approximately one hour before the patient noted the sounds over the heart. This is the story one would expect with a rupture of an alveolus and dissection back along the vascular channels bringing on the original pain. With the arrival of the air in the mediastinum the heart signs then become evident.

Case 4. A 20 year old white male was admitted to the hospital on June 24, 1944, complaining of pain in the chest and shortness of breath. On the previous day while playing tennis he had suddenly experienced a severe pain in the left upper and right lower chest posteriorly, as he was raising his left arm in order to serve. The pain was aggravated by attempts at deep inspiration. At the same time, he felt "dizzy," as if he were going to faint. He had slight dyspnea and cough. He immediately stopped playing and went to bed. He fell asleep, despite the persistence of the pain, but was awakened by inability to "catch his breath." This was relieved only by sitting up in a "hunched-over" position. After half an hour of sitting in this position he was able to fall asleep again. The next day pain persisted and patient was aware of gurgling sounds in his left chest.

On examination, he was found to prefer lying on his left side. He appeared to be in no distress. A few fine râles were heard along the lower left border of the sternum and in the left posterior chest at the level of the ninth and tenth thoracic vertebrae. At the cardiac apex and synchronous with the heart beat was a characteristic "crunching murmur." Roentgen-ray examination of the chest revealed a left apical pneumothorax with about 15 per cent collapse of the lung. Leukocyte counts and urinalyses were normal.

At bed rest the patient's pain quickly subsided, although the crunching sounds continued to be heard for two weeks. The temperature remained normal. Two weeks after admission he had a recurrence of severe pain in the left anterior chest and in the epigastrium with an increase in the number of crackling sounds heard over the heart. For several days he continued to have a sense of tightness in his epigastrium, and then all discomfort and physical signs gradually disappeared. He was discharged to duty on August 2, six weeks after admission, roentgen-ray examination having shown complete resorption of air.

Comment. This is another typical instance of spontaneous mediastinal emphysema, although the patient was indulging in heavy physical exercise at the time of its onset. He apparently had a mild recurrence while at bed rest. The epigastric pain and discomfort suggested retroperitoneal extension of the air at the time of the recurrence.

Case 5. A 21 year old white male was admitted to the hospital on August 15, 1944 complaining of pain in the left chest and shortness of breath. On the previous day while walking along the street he was suddenly seized with a sharp pain in the lower left chest, with radiation to the precordium and the left shoulder. He was unable to take a deep breath without intensifying the pain. His symptoms persisted until the morning of admission. At this time he was able to take a deep breath only when in a sitting position.

Physical examination showed the patient to be in no acute distress. The amplitude of excursions of the left thorax was diminished. Breath sounds and vocal and

tactile fremitus were also diminished on this side. A few "crackling" sounds were heard in an area one to two inches to the left of the mid-sternum. Roentgenographic examination of the chest showed a left pneumothorax with 60 per cent compression of the upper lobe and 30 per cent compression of the lower lobe. There was a moderate mediastinal herniation to the right. Leukocyte counts were normal.

Two days after admission "gurgling and crackling" sounds were heard over the heart, and in addition numerous metallic tapping sounds of a different character were noted in the same area. The patient's pain subsided almost immediately with the institution of rest and the adventitious sounds of both types gradually diminished until September 11, about four weeks after admission, the roentgen-ray examination was negative, and no further abnormal sounds were heard. The remainder of the hospital stay was uneventful and the patient was discharged to duty on October 30.

Comment. The pneumothorax in this case was of greater extent than in the previous cases, and it was possible to distinguish two entirely distinct types of adventitious sounds over the heart. One was the crunching or bubbling type as heard in the previous cases, whereas the second was of the metallic knocking type, which Greene has pointed out is associated with a left pneumothorax occasionally.

Case 6. A 23 year ol white male soldier was admitted to the hospital on September 6, 1944, with a hist ry of recurrent attacks of left anterior chest pain since December 1943. The pain first made its appearance while the patient was running and lasted for several hours. Since that time the pain had recurred about five times a month and usually lasted about half a day each time, although on one occasion it persisted for two days. Physical training and running were the most frequent precipitating factors. The patient also had considerable belching and attributed his symptoms to "gas." He was an aviation cadet, and when he started flying the attacks increased in frequency, although they did not necessarily come on while he was flying. He also began to have headaches with the attacks. Both belching and headaches were aggravated directly while he was flying. He was hospitalized at another hospital in July 1944 and was told that he had a heart murmur, but that the pain in the chest was due to a "strained muscle." He was eliminated from cadet training and was grounded.

The frequency of attacks became less after he was grounded, but he still had them in a fairly mild degree several times a month.

One hour before the present admission while standing in a line at the mess he experienced the most severe pain of all. It was sudden, was felt in the anterior aspect of the left chest, and made him want to "double up." No cough or shortness of breath accompanied the pain, but he did have a sense of palpitation.

Examination showed him to be irritable and depressed, but only moderately uncomfortable from the pain. Excursions of the left chest were limited, and there were diminished heart sounds and hyperresonance on this side. Blood pressure was 136 mm. Hg systolic and 80 mm. diastolic. On the day of admission, no adventitious sounds were heard over the heart and the diagnosis of left spontaneous pneumothorax was made. On the following day, however, numerous crunching and crackling sounds were heard over the heart. On the next day, they again were not elicited, but from then on sounds described as "tissue paper crackling" were heard for two weeks.

Roentgen-ray examination of the chest on the day after admission showed a left pneumothorax with an upper lobe collapse of about 50 per cent and a lower lobe collapse of about 25 per cent. There was moderate thickening of the visceral pleura over the upper lobe with a small adhesion over the apex. There was no mediastinal shift.

Three days later the roentgen-ray examination showed considerable reëxpansion of the lung. The upper lobe was only 40 per cent compressed, and the lower lobe had almost completely reëxpanded. At this time there was a moderately dense line parallel to the left border of the heart and about 0.5 cm. distance from it. An area of increased radiolucency was present between this line and the cardiac border. This was best observed in the region of the cardiac waist.

Leukocyte counts and electrocardiograms were normal.

The patient's symptoms quickly subsided and after four weeks there were no abnormal physical or radiographic signs.

Comment. This case is of particular interest for several reasons. First, it illustrates the necessity of searching carefully for the signs of mediastinal emphysema in every case of pneumothorax. Both the initial physical and roentgenographic examinations elicited only signs of a pneumothorax. Second, although the long previous history of recurrent chest pain, headache, and belching is difficult to interpret precisely (functional symptoms cannot be excluded), the possibility is suggested that this is an instance of repeated attacks of mediastinal emphysema. The similarity to case 2 should be noted. These two cases suggest that in certain cases mediastinal emphysema may appear to run a chronic course different from the classical description of a sudden acute attack with quick complete recovery after bed rest. If this interpretation is accepted, the exacerbation of symptoms by flying would confirm the observations of Lovelace and Hinshaw.[24]

Case 7. An 18 year old white male was admitted to the hospital October 8, 1945 complaining of pain in the right lower chest. The pain had appeared suddenly on October 7 without exertion and persisted until the time of admission. The pain was aggravated by breathing. There was no cough and no respiratory infection. Three weeks previously, after returning from a hike, he had experienced a similar attack of pain in the right chest. He rested in his quarters for a half day and had no more pain until the present attack. Family and past history were otherwise non-contributory.

Physical examination on admission showed a well nourished boy complaining of pain in the right chest. The lung fields were normal to auscultation and percussion. Over the mid sternum were heard clicking, crunching sounds systolic in time and varying with respiration.

Roentgen-ray examination on the third hospital day showed a small right apical pneumothorax. Hemoglobin, erythrocyte, leukocyte, and differential counts were normal. Urine examination was normal. Sputum culture showed only alpha streptococci. Sedimentation rates were normal throughout his hospital stay. Electrocardiograms were within normal limits. Temperature, pulse and respiratory rates were not abnormal.

The pain was relieved by bed rest. The typical sounds over the sternum were heard in diminishing intensity for one week. On the tenth hospital day roentgen-ray examination of the chest showed complete reëxpansion of the lung with no evidence of pulmonary disease. He was discharged to duty after 22 days in the hospital.

Comment. This case represents a typical acute mediastinal emphysema. It is probable from the history of a similar attack three weeks before that this episode was a recurrence. It is interesting that in this case we observed a right apical pneumothorax. It is unusual, for in most cases reported the small pneumothorax occurs over the left apex.

Discussion

These seven cases illustrate some of the problems of diagnosis and prognosis in acute mediastinal emphysema. The one certain diagnostic sign is the occurrence of crunching, crackling, popping sounds over the heart. Once heard they can be confused with no other cardiac sounds. The development of subcutaneous emphysema of the neck confirms the diagnosis. Every patient with a spontaneous pneumothorax, especially if it is small, should be carefully examined for the presence of mediastinal emphysema. One of our patients was thought to have only a spontaneous pneumothorax until reexamination the day after admission revealed the typical sounds over the precordium. Once one is familiar with the syndrome it should not be difficult to differentiate it from other diseases. The two diseases most commonly confused are acute pericarditis and coronary occlusion with myocardial infarction. Careful auscultation of the heart will establish the correct diagnosis.

The dangers of recurrence in this condition have not been stressed in previous reports. Apparently it is an important problem. One of our cases had a recurrence four weeks after his original attack. Two others had either recurrent attacks or a slow leak of air which gave almost constant symptoms for six to nine months. A fourth had a recurrence while at bed rest. A fifth had a previous episode from the history.

We feel the treatment should consist of prolonged bed rest until healing of the rupture is assured. We also administered sulfadiazine in moderate dosage for several days as a prophylactic against mediastinitis. This complication has not been reported, but it seems a possibility with a connection between the respiratory tract and the mediastinum especially if there is an associated respiratory infection.

Summary

1. Seven cases of mediastinal emphysema are presented. One was associated with an acute respiratory infection and bronchial asthma, and six were spontaneous.

2. Five cases experienced a recurrence of this condition, and in two of these there were prolonged symptoms over six to nine months.

3. All six spontaneous cases had an associated pneumothorax. The necessity for careful examination of the precordium for mediastinal emphysema in cases with a small left apical pneumothorax is emphasized.

4. The clinical picture and problems of diagnosis and treatment are discussed.

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STUDIES ON TWO SPORADIC CRETINOUS BROTHERS WITH GOITER, TOGETHER WITH SOME REMARKS ON THE RELATION OF HYPERPLASIA TO NEOPLASIA *

By J. LERMAN, M.D., H. W. JONES, M.D., and E. CALKINS, M.D.,
Boston, Massachusetts

OUR interest in the pathology and pathological physiology of cretinous goiters was stimulated by the discovery and study of two cretinous brothers, both possessing goiters. The results of this study, plus additional observations on two other cretinous subjects with goiter, on patients treated with thiouracil and on experimental animals, have been the basis of speculation regarding the rôle of hyperplasia in the genesis of neoplasia. Since studies of the type made on the two cretinous brothers are instructive, the results are presented below in detail, together with brief clinical histories.

CASE REPORTS

Case 1. R. W., a 19 year old white boy, was admitted to the Massachusetts General Hospital on October 4, 1944. He complained of a mass which had been present in his neck for seven years. He had apparently been essentially well and normal until the age of 10, when his mother remarked about his failure to grow. When he was 12 years old his mother noticed a swelling in his neck. The goiter increased in size until it reached the dimensions of a lemon. He was given thyroid ½ grain (0.032 gram) and later 1 grain (0.065 gram) daily. He grew rapidly between the ages of 13 and 15, the size of the thyroid mass meanwhile remaining stationary. At 17, thyroid medication was discontinued, and the goiter began to enlarge again, eventually reaching the proportions of a large orange on each side.

Pubic hair began to appear when the patient was 16. Voice changes were first noted one month prior to admission. He left school at the age of 16 when in the fifth grade, and has since worked at many jobs but never lasted long in any because he was slow in his work.

The patient was born in Leister, Massachusetts, and lived in New Jersey and Maine for short periods. Since the age of five he has lived in Worcester, Massachusetts. The diet was adequate and did not include excessive amounts of goitrogenic foods such as cabbage and soy beans. There was no family history of endocrine disease. There were three siblings: a normal male, age 14; a male, C. W., age 12, presented below; and a normal female, age 4.

On physical examination the patient appeared well-proportioned and muscular (figure 1). He was 64 inches (163 centimeters) tall and weighed 139 pounds (63 kilograms). The skin was dry, rough, and pale. The hair was not remarkable. The eyes were set wide apart, the bridge of the nose was flat and the nostrils wide and flaring. The voice was husky. The thyroid was symmetrically enlarged, measuring 15 by 8 centimeters, firm in consistency, and without bruit.

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From the Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts.

Laboratory findings are in part listed in table 1. The urine and blood counts were normal. The bone age, as determined from roentgen-ray examination of the hands, was 18 years and three months, of the iliac crest, 17 years. The mental age was 10 years six months. The various chemical studies on the blood, the excretion of follicle-stimulating hormone (F.S.H.) and of the 17-ketosteroids in the urine, the glucose-tolerance test, the insulin-tolerance test, the Keppler water-diuresis test and the basal metabolism level of minus 28 were all consistent with his myxedematous state. The blood cholesterol, surprisingly enough, was normal—169 mg. per cent. There was no detectable amount of thiocyanate in the blood. When a tracer dose of radioactive iodine was administered to the patient, the goiter retained 87 per cent, indicating that the goiter had a strong avidity for iodine. The iodine content of the gland, as determined on a biopsy specimen, was low, namely 0.07 per cent.

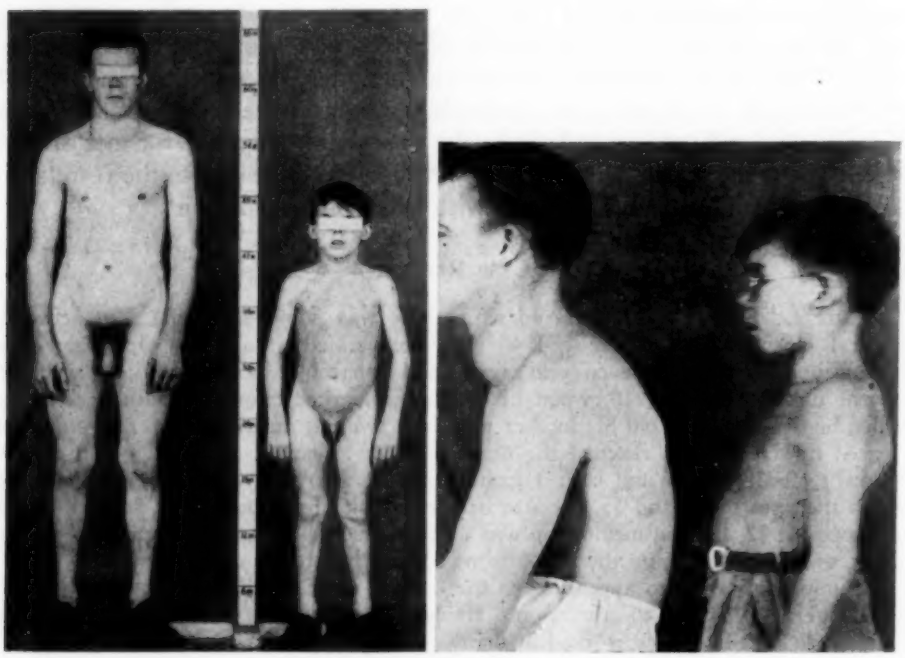

FIG. 1. Antero-posterior and lateral view of two cretinous brothers, R. W. on the left and C. W. on the right of each view.

Histological examination of the biopsy specimen revealed a highly vascular tissue with loose arrangement in follicles and cords of varying size, mostly small, and a small amount of interstitial connective tissue (figure 2). The epithelium was high cuboidal to columnar and there was a small amount of colloid. Mitoses were not observed. The diagnosis was struma nodosa micro and macro folliculare.

Case 2. C. W., a 12-year old schoolboy, was admitted to the Massachusetts General Hospital at the same time as his brother R. W. At the age of five, he was found to have a goiter, at the same time it was discovered in his brother, and he, too, was placed on thyroid, ½ grain (0.032 gram) at first and later 1 grain (0.065 gram) daily. Thyroid was discontinued in January 1943 when the basal metabolism was found to be plus 9. During the period of thyroid medication the goiter did not enlarge further but body growth was very slow. After thyroid was discontinued, the mass in the

TABLE I

Laboratory and Other Data on Two Cretinous Brothers with Goiter

	Case 1 (*R.W.*)	Case 2 (*C.W.*)
Age	19 years	12 years
Bone age (hands)	18¾ years	5¾ years
Mental age	10½ years	8⅛ years
Electrocardiogram	normal	normal
Chest roentgenogram	normal	normal
Blood cholesterol	169 mg. %	183 mg. %
Blood calcium	9.3 mg. %	9.0 mg. %
Blood phosphorus	2.5 mg. %	4.9 mg. %
Blood alkaline phosphatase	2.4 units	3.7 units
Blood sodium	137.5 m.eq./L.	138.8 m.eq./L.
Blood chloride	101.0 m.eq./L.	101.4 m.eq./L.
Serum protein	7.1%	6.7%
Glucose tolerance	*Blood Sugar*	*Blood Sugar*
Fasting	74 mg. %	80 mg. %
½ hour	98	111
1 hour	118	114
2 hours	87	114
3 hours	95	103
4 hours	89	89
5 hours	98	95
Insulin tolerance		
Fasting	100 mg. %	93 mg. %
20 minutes	67	65
30 minutes	75	63
45 minutes	80	68
60 minutes	75	—
90 minutes	82	63
120 minutes	87	61
(epinephrine 0.5 c.c. s.c.)		
45 minutes	100	103
60 minutes	118	95
F.S.H. excretion	pos. 6.5 m.u./24 hrs.	pos. 3 m.u./24 hrs
17-ketosteroid	3.6 mg./24 hrs.	0.9 mg./24 hrs.
Keppler water-diuresis test	negative	negative
B.M.R. level	minus 28	minus 20
Collection of radio-iodine by gland	87%	58%
I_2 content of gland	0.07%	——

neck increased in size, the skin became rough and the abdomen gradually became distended. He gained 10 pounds in the year preceding admission but did not increase in height. He walked slowly, seldom played games and was intolerant of the cold. He was slightly retarded mentally, being in the fifth grade at the time of admission. As in the case of his brother he had lived in Worcester, Massachusetts all his life and his diet was not excessive in any known goitrogenic foods.

On physical examination the patient appeared small and underdeveloped, with cretinoid facies (figure 1). He was 48 inches tall and weighed 54 pounds. The skin was warm, pale, and hyperkeratotic, especially over the abdomen. The thyroid was diffusely and moderately enlarged, consisting of soft, nodular tissue, more in the right lobe than in the left lobe; a bruit was not audible. The tongue was smooth and the voice hoarse and rather deep. The abdomen was protuberant and contained many fecal impactions.

The important laboratory findings in this case are also summarized in table 1. He had a slight anemia of 3.09 million red cells and 12 grams of hemoglobin. The urine was normal. The bone age was five years nine months, as determined by roentgen-ray examination of the hands; five years by examination of the femoral heads. The mental age was eight years and two months. As in Case 1, the various chemical determinations on the blood, the excretion of follicle-stimulating hormone

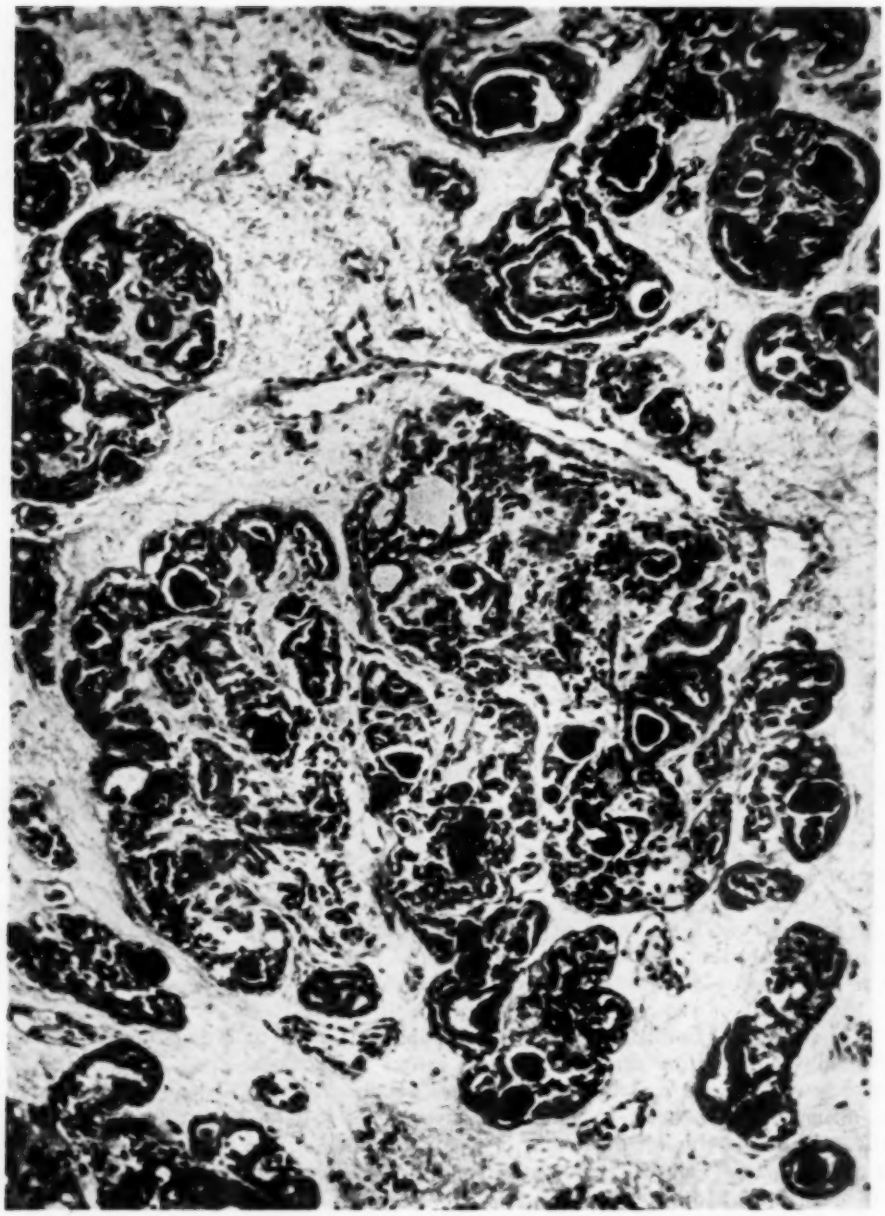

FIG. 2a. Low power view of a section of thyroid tissue from Case 1 (R. W.).

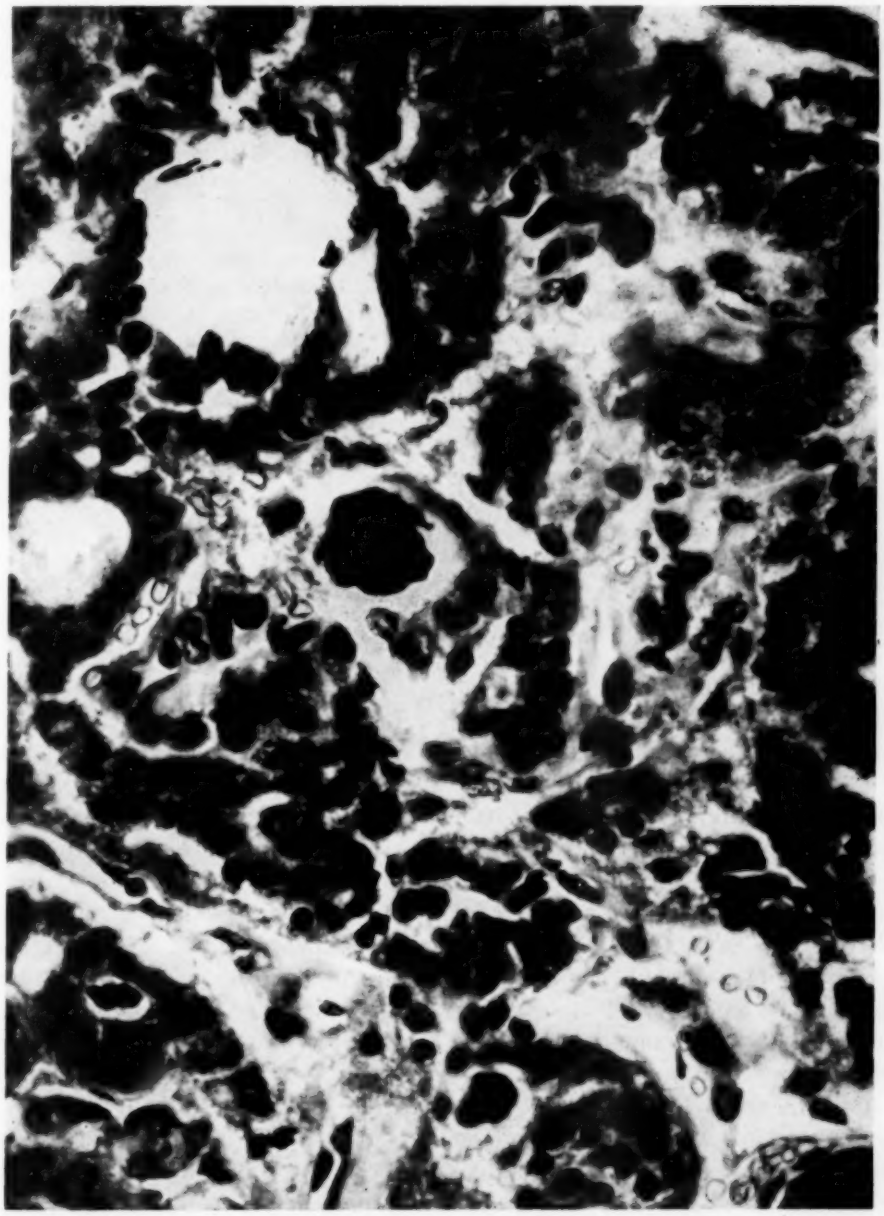

FIG. 2*b*. High power view of a section of thyroid tissue from Case 1 (R. W.).

(F.S.H.) and of the 17-ketosteroids in the urine, the glucose-tolerance test, the insulin-tolerance test and the Keppler water-diuresis test were all consistent with his cretinoid state. Again there was no detectable amount of thiocyanate in the blood. The metabolism varied considerably, reaching levels as low as minus 24, but averaged minus 20. The collection by the thyroid of a tracer dose of radioactive iodine amounted to 58 per cent.

Examination of a biopsy specimen of the thyroid disclosed a loose arrangement of glandular tissue in columns and clusters of cuboidal cells. The tissue was highly vascular and there was no colloid present (figure 3). The diagnosis was fetal adenoma.

The diagnosis of cretinism in these two cases seems to be well established. Their general appearance is strongly suggestive. The low metabolism, the retarded bone age, the retarded mentality and the various chemical and biological tests are all confirmatory. The normal blood cholesterol is a little disturbing. The low values for the excretion of follicle-stimulating hormone (F.S.H.) and of the 17-ketosteroids in the urine in Case 2, although consistent with cretinism, favors the diagnosis of hypopituitarism. However, the character of the insulin-tolerance test and the negative Keppler water-diuresis test argue for thyroid deficiency.

After a short period of iodine medication, both glands were removed. The histological sections revealed two interesting findings: (1) the pathological changes in the two specimens were similar; (2) the changes were not uniform. There were areas in each gland characteristic of fetal adenoma; other areas were typical of papillary cyst adenoma, of struma nodosa macro and micro folliculare and of colloid goiter (see figures 4 and 5).

Discussion

In an endemic goiter area, a cretin with goiter is common; in a non-goiterous area, a cretin with goiter is rather rare. When present it must represent the result of the effort made by the gland to produce more hormone. The biological studies in these two cases, which indicate a low iodine content of the goiter (0.07 per cent) and a strong avidity for iodine, are consistent with an iodine-deficiency goiter. These findings agree with those of Hamilton, Soley, and Reilly [1] who found that the glands of eight cretin patients with atrophic thyroids took up less radioactive iodine than normal, whereas two goiterous thyroids took up excessive amounts. It is hard to visualize how iodine-deficiency can develop in this region. However, the ingestion of a positive goitrogen may also account for this type of goiter. In fact, low iodine-content and high iodine-uptake are found in sulfocyanate and cabbage goiters as well as in iodine-deficiency goiters (see Rawson, Tannheimer and Peacock [2]). As far as it could be determined, the diet of these two boys was apparently adequate in iodine and not excessive in cabbage, soy beans or related vegetables. To be sure, an unknown goitrogen cannot be ruled out. In any case, the gland, under these circumstances, should show hyperplasia. The actual changes in the gland were those which Marine and Lenhart [3] associated with the process of hyperplasia. Some areas showed regression to colloid goiter; other areas consisted of solid cords of young cells, without tendency to follicle formation and with very little supporting structure, and of structures characteristic of papillary cyst ade-

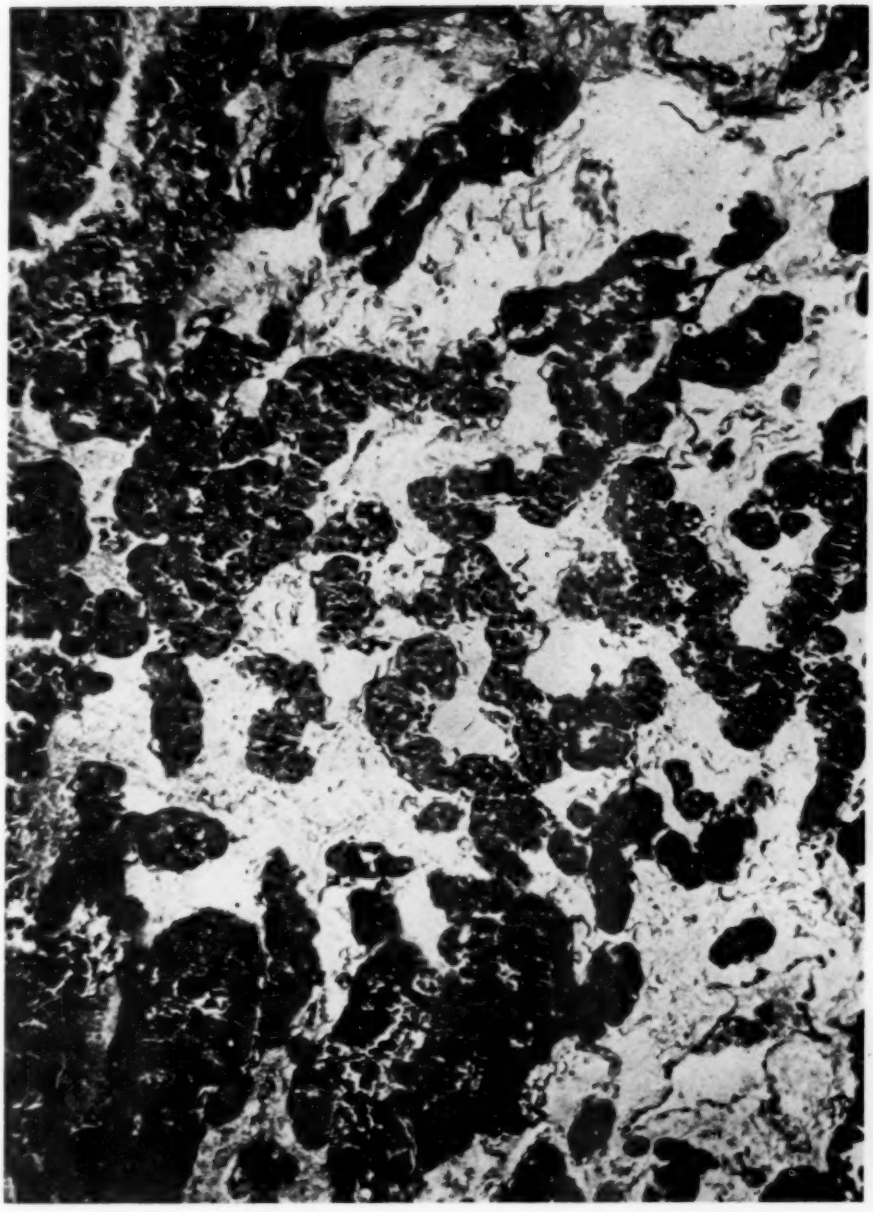

FIG. 3*a*. Low power view of a section of thyroid tissue from Case 2 (C. W.).

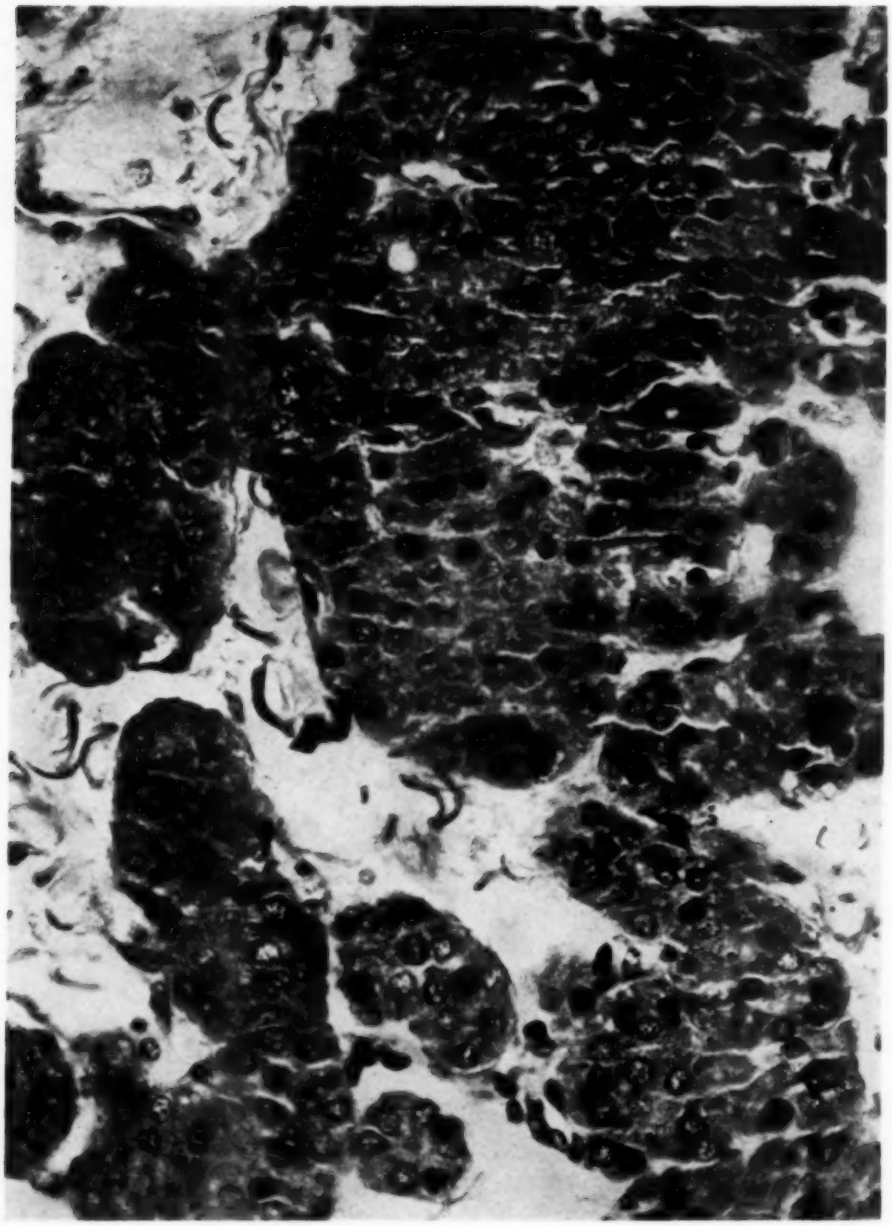

FIG. 3*b*. High power view of a section of thyroid tissue from Case 2 (C. W.). Note the solid cords of tissue with very little supportive structure.

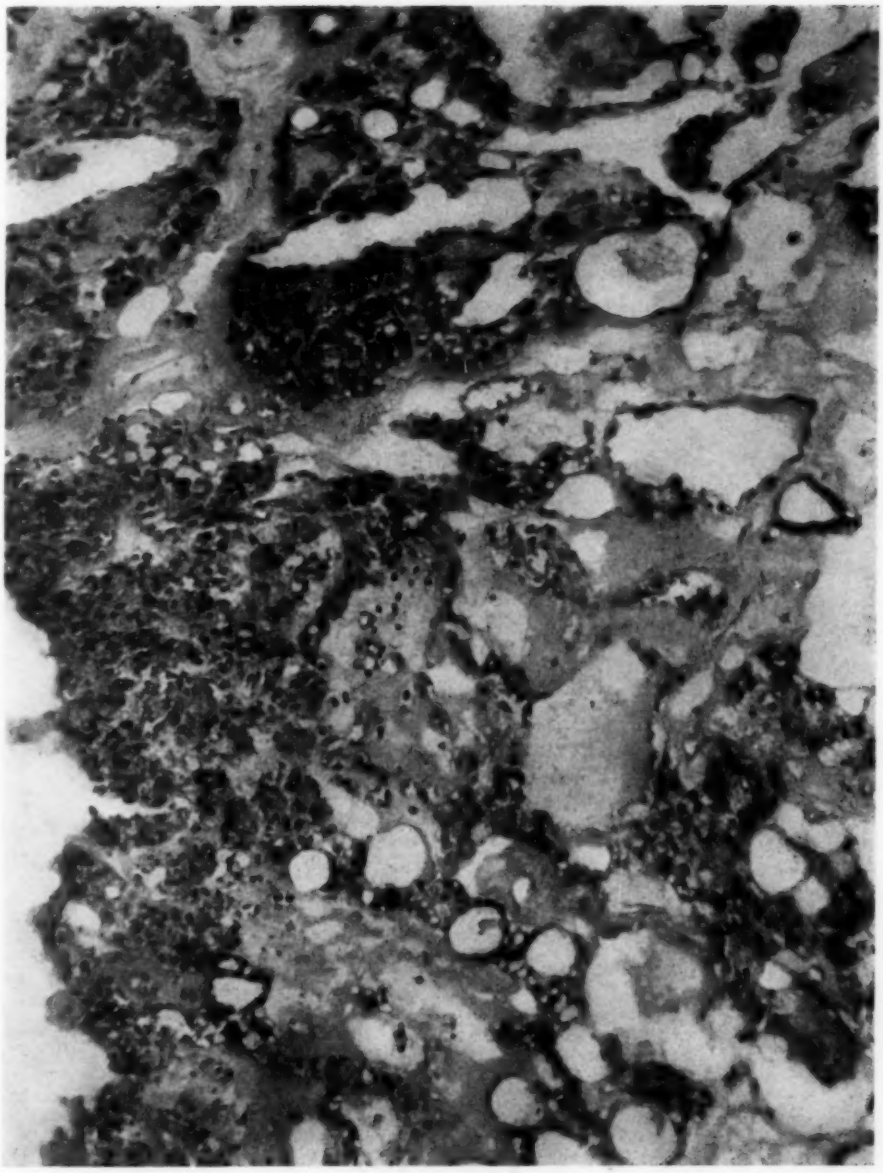

FIG. 4*a*.

FIG. 4*b*.

FIG. 4*c*.

FIG. 4. Three low power views of thyroid removed at operation in Case 1 (R. W.): (a) fetal adenoma; (b) papillary cyst adenoma; (c) colloid goiter tissue.

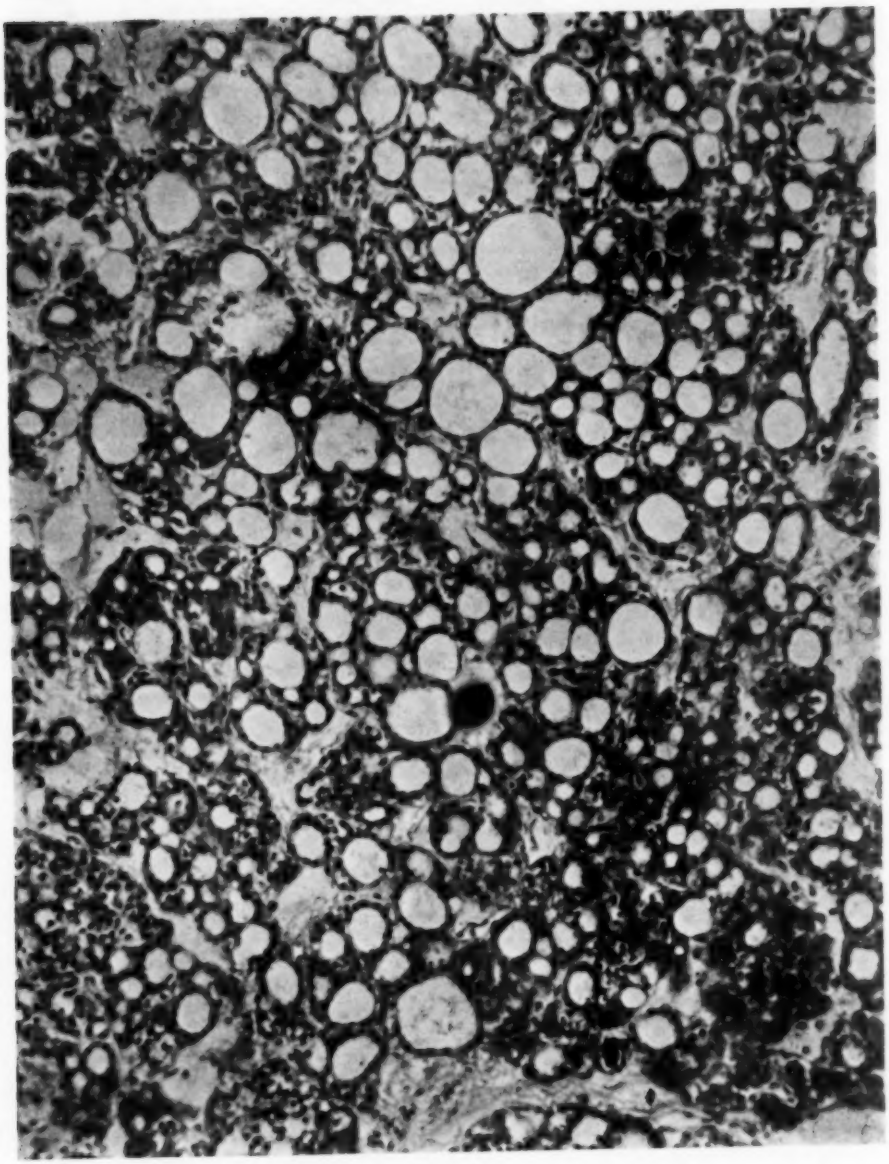

FIG. 5*a*.

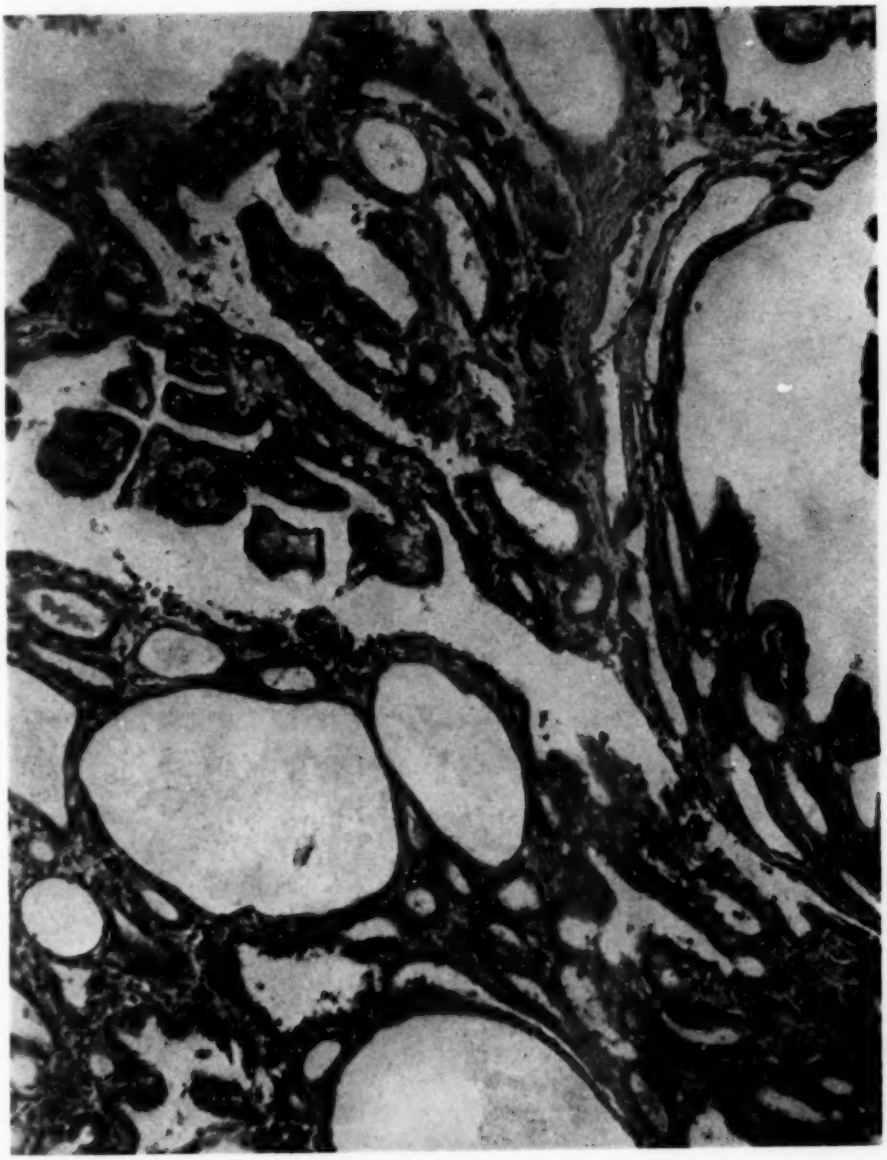

FIG. 5*b*.

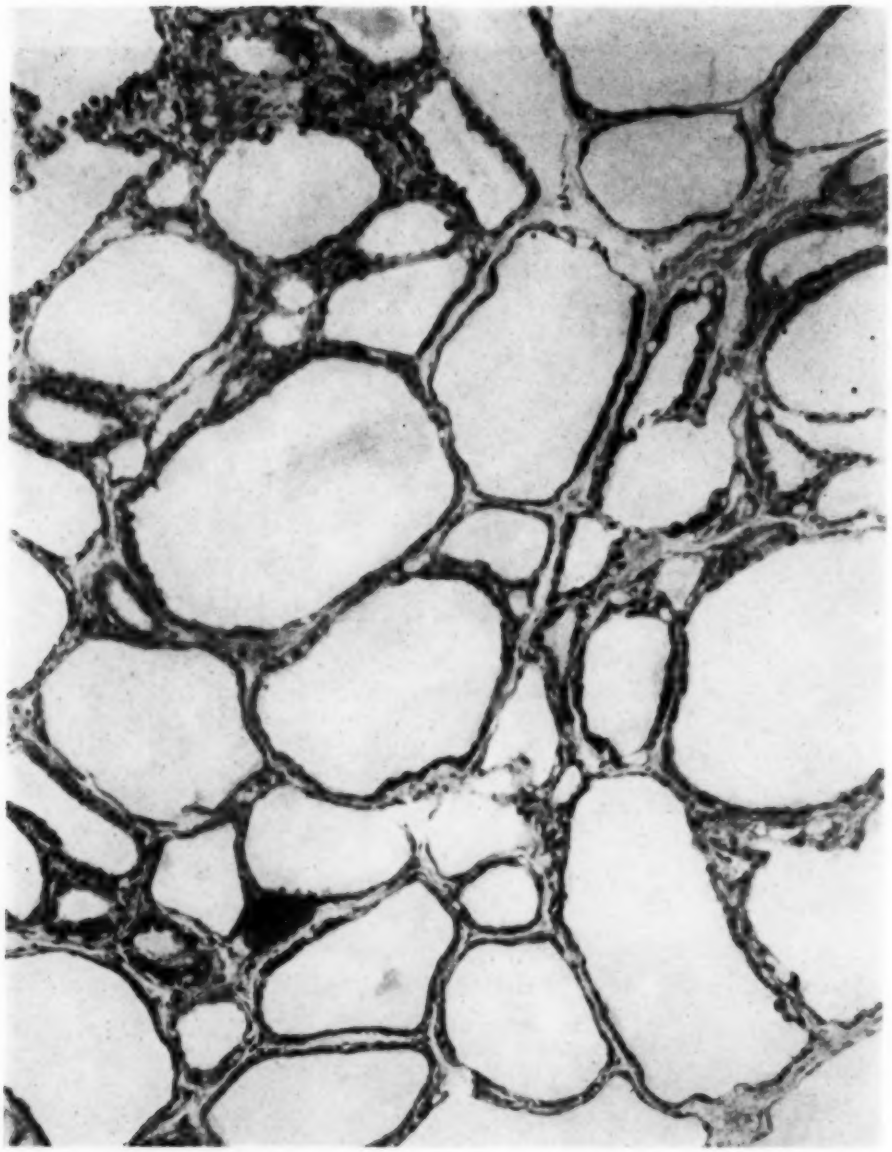

FIG. 5c.

FIG. 5. Three low power views of thyroid removed at operation in Case 2 (C. W.): (a) Struma nodosa macro and micro folliculare; (b) papillary cyst adenoma; (c) colloid goiter tissue.

noma. Both types are quite suggestive of pre-neoplastic or neoplastic changes.

These unusual findings led us to reëxamine the records of two other cretins with goiter seen in 1942. One was a 13 year old boy (H. E.) living on the seacoast of Massachusetts, and was one of seven siblings, four of whom were cretins, two with and two without goiters. He had received thyroid and iodine for many years, but finally the gland, weighing 240 grams, was removed. The gland was extremely vascular and microscopically resembled the gland of C. W. (see figure 6). The other was a 21 year old girl (D. B.) who had a subtotal thyroidectomy for a nodular goiter weighing 160 grams. The tissue contained very little iodine, namely 0.01 per cent, and its microscopic structure simulated that of the gland from R. W. (see figure 7).

Two other bits of information are pertinent here. Recently we had the opportunity to examine sections of pigs' thyroids sent to Dr. R. W. Rawson by Dr. F. N. Andrews of Purdue University. These thyroids were removed from the offspring of pigs which had been fed a soy bean diet. These offspring were cretinous and had goiters which contained very little iodine (0.006–0.01 per cent). Some of these thyroids showed extensive hyperplasia (figure 8); others showed a structure not unlike struma nodosa macro and micro folliculare; and still others showed the solid structure of fetal adenoma (figure 9).

In ordinary Graves' disease, when thiouracil is administered for two or more weeks, the gland at operation shows a high degree of hyperplasia. In some cases in which thiouracil is administered for six weeks or longer before operation, the gland shows areas resembling the structure of fetal adenoma as well as areas of hyperplasia. In one instance in which thiouracil was administered for 10 months, the entire gland showed a microscopic appearance characteristic of struma nodosa macro and micro folliculare (figure 10).

These findings raise anew several questions regarding the relationship between hyperplasia and neoplasia. Is neoplasia the end-result of severe and extensive hyperplasia? What is the significance of apparently neoplastic changes in a gland which is clinically benign? Finally, what is the rôle in the pathogenesis of malignancy of agents which increase hyperplasia? A smattering of experimental and clinical data is available. Hellwig [4] placed six white rats on a high calcium, low iodine diet. Hyperplasia occurred in all and in two, definite adenomata of the lobular, small follicle type. He believes that adenomata arise as a local hyperplasia of the epithelium, and that they represent an intermediate stage between hyperplasia and malignancy. The recent experimental observations by Bielschowsky [5] are most illuminating. He observed that 2-acetyl-amino fluorine, when fed alone, caused malignant tumors of various organs in rats but never in the thyroid, whereas allyl-thiourea resulted in hyperplasia of the thyroid, but never neoplasia.

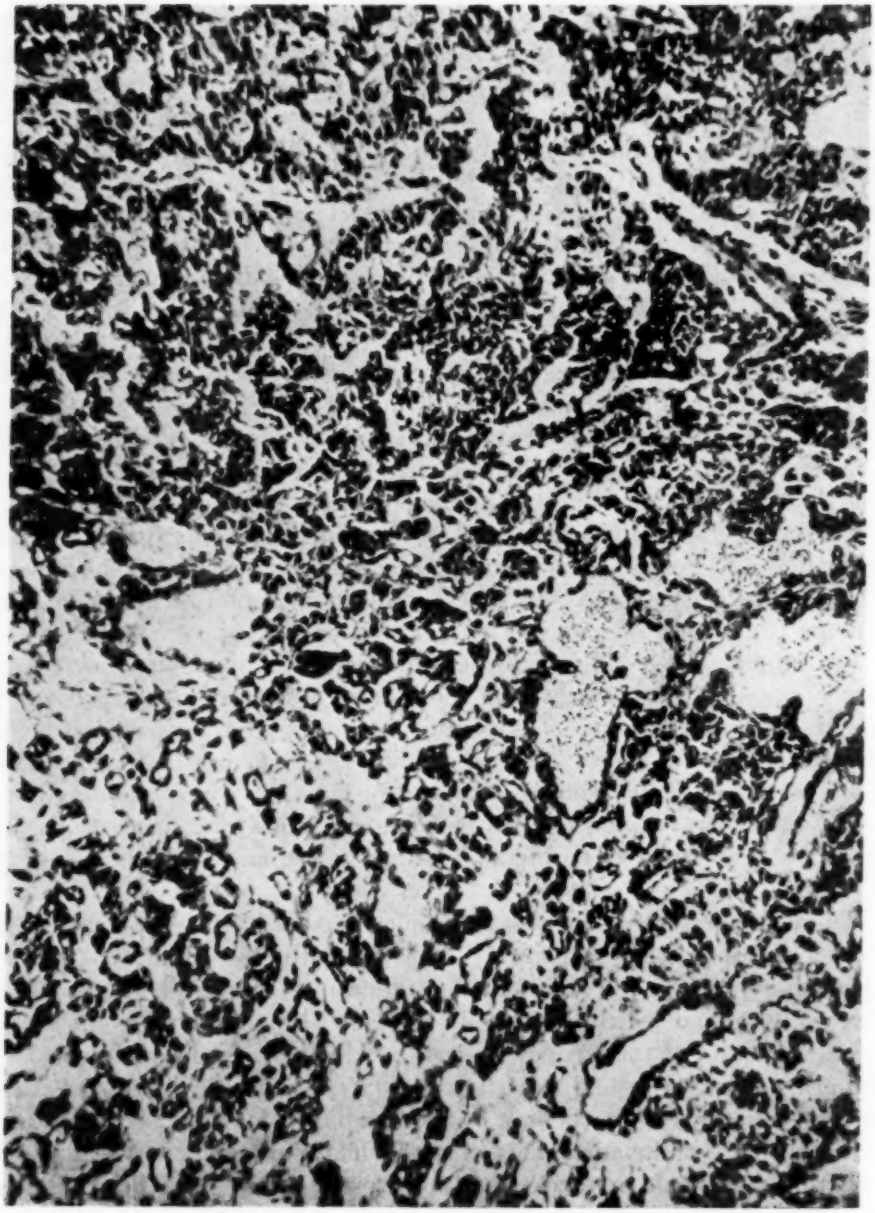

FIG. 6a. Low power view of a section of thyroid tissue from patient H. E.

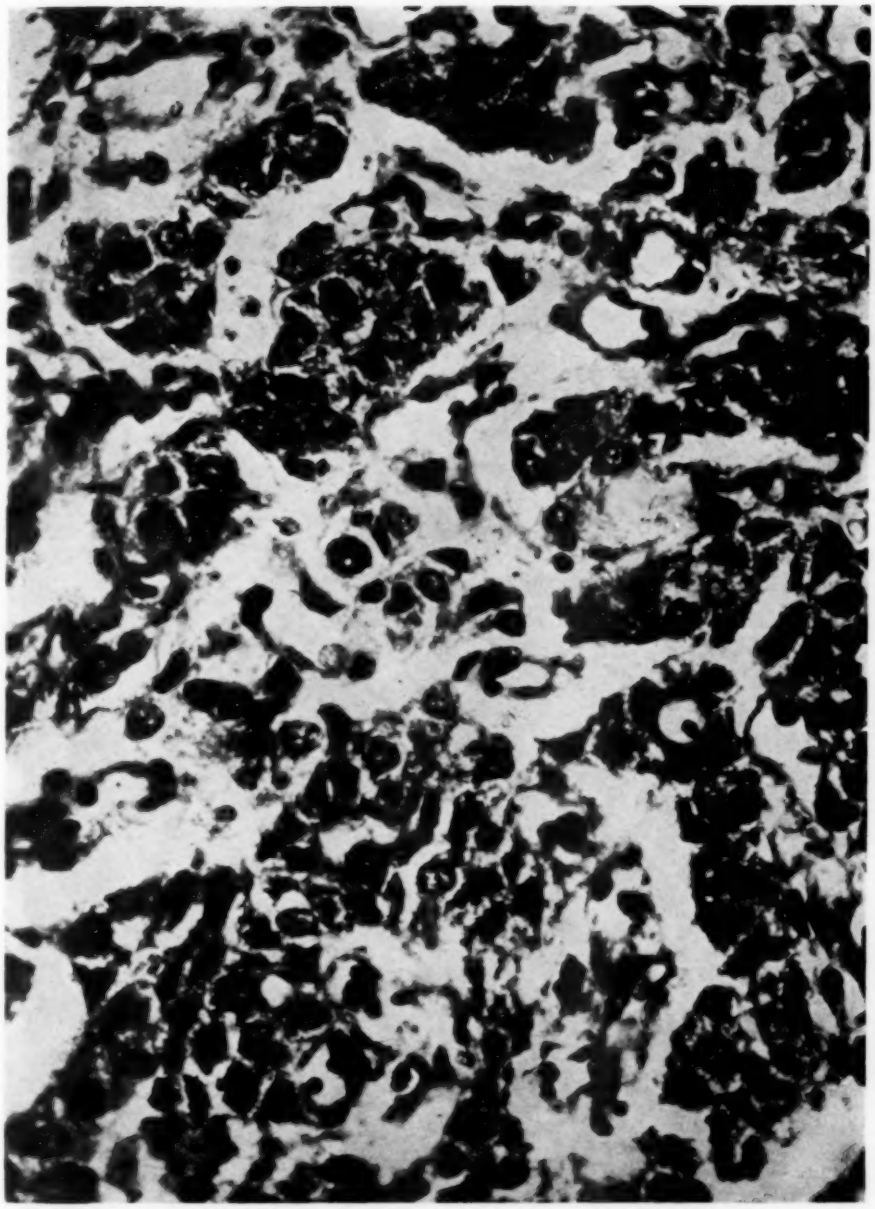

FIG. 6*b*. High power view of a section of thyroid tissue from patient H. E.

FIG. 7*a*. Low power view of a section of thyroid tissue from patient D. B.

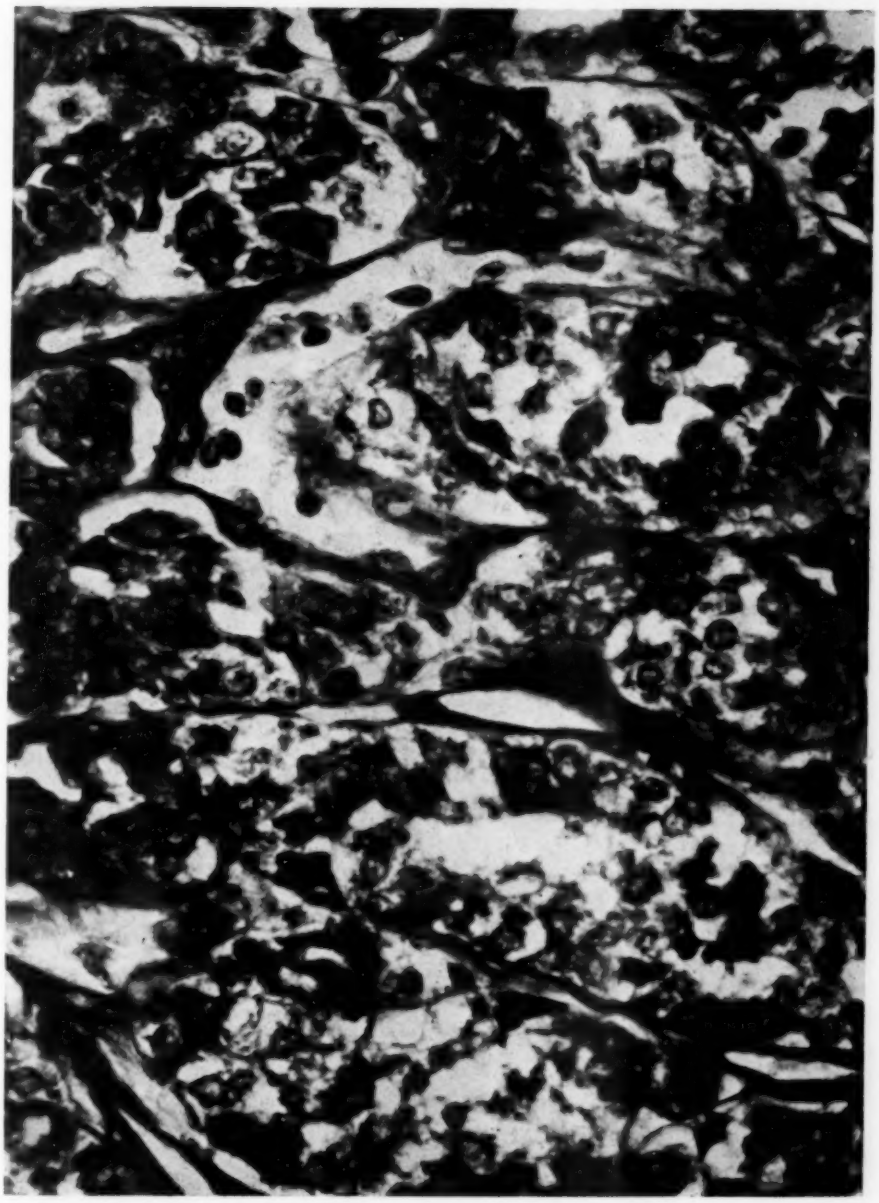

FIG. 7*b*. High power view of a section of thyroid tissue from patient D. B.

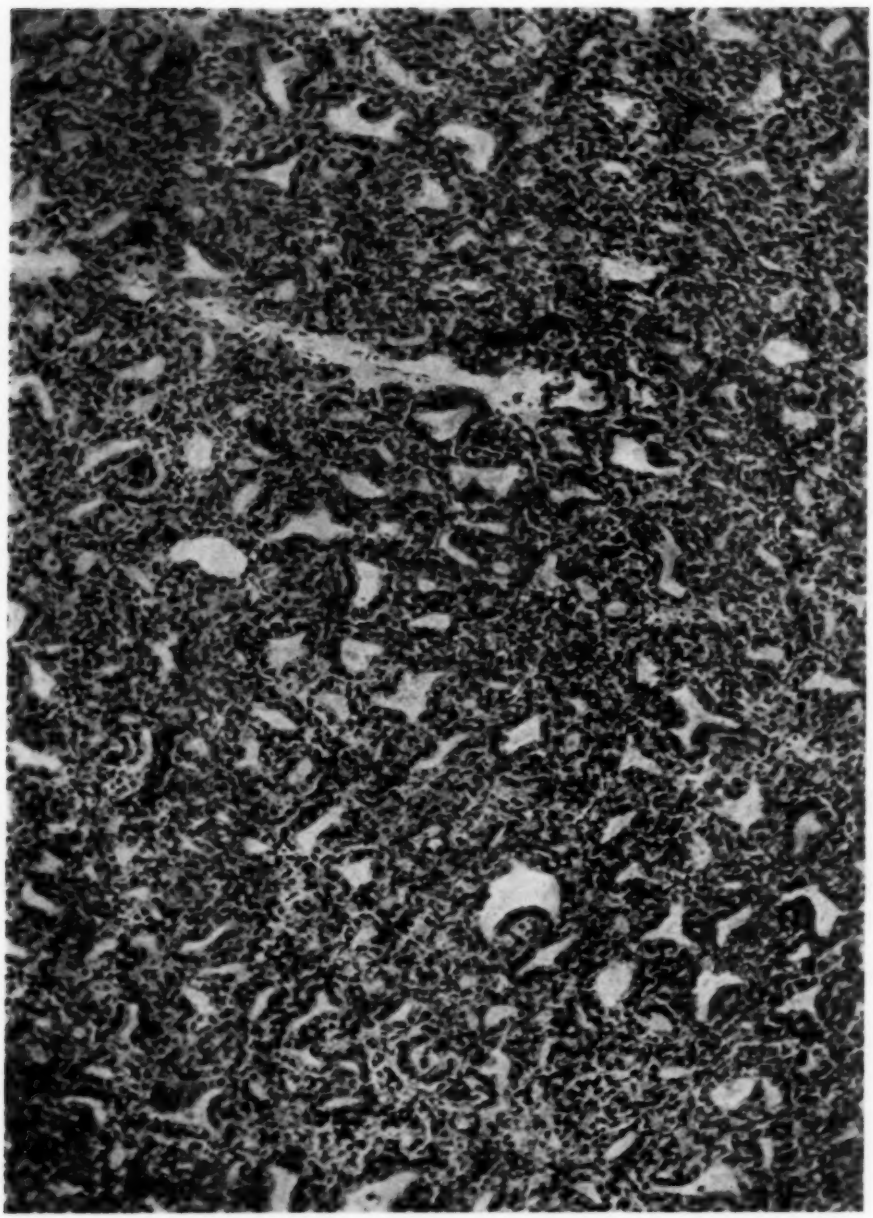

FIG. 8*a*. Low power view of a section of thyroid tissue from a cretinous pig, whose parents were on a soy bean diet.

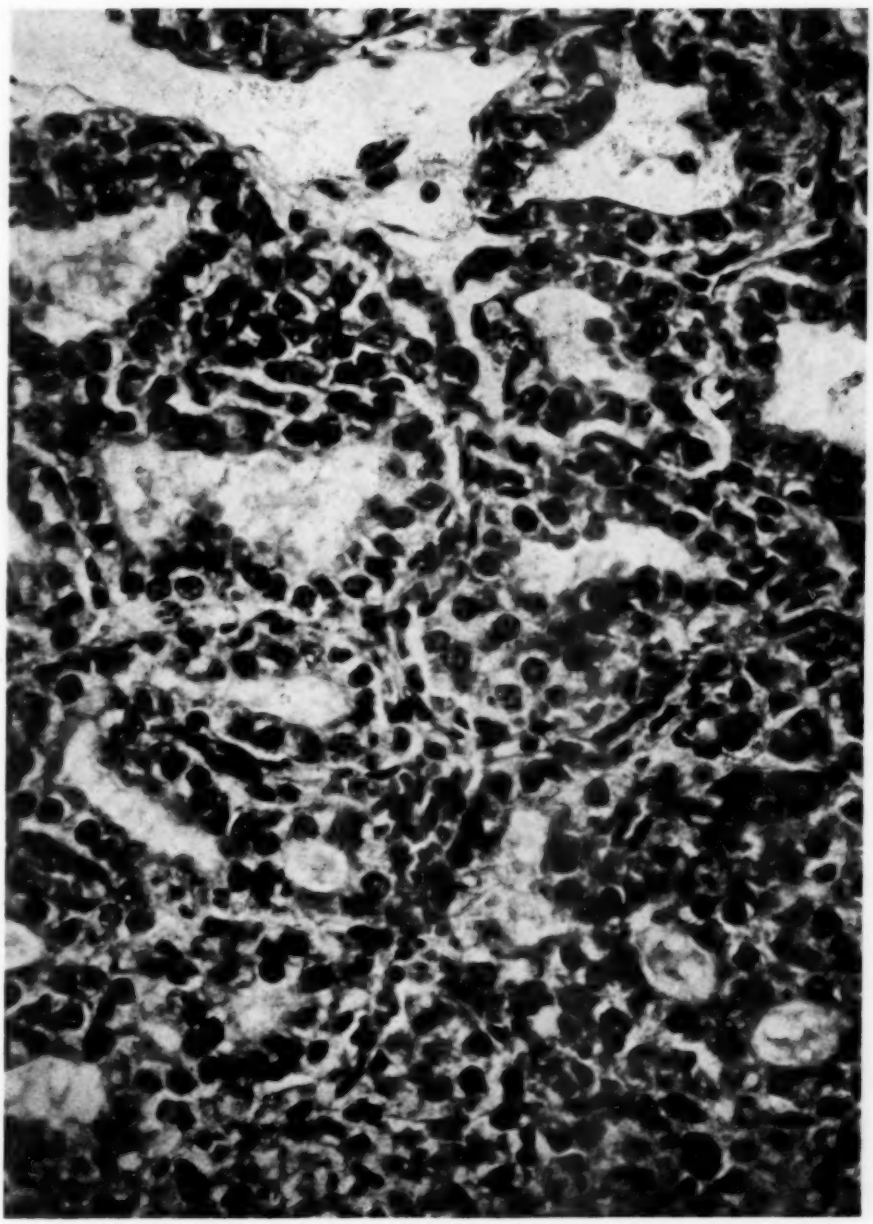

FIG. 8*b*. High power view of a section of thyroid tissue from a cretinous pig, whose parents were on a soy bean diet. Note the extensive hyperplasia.

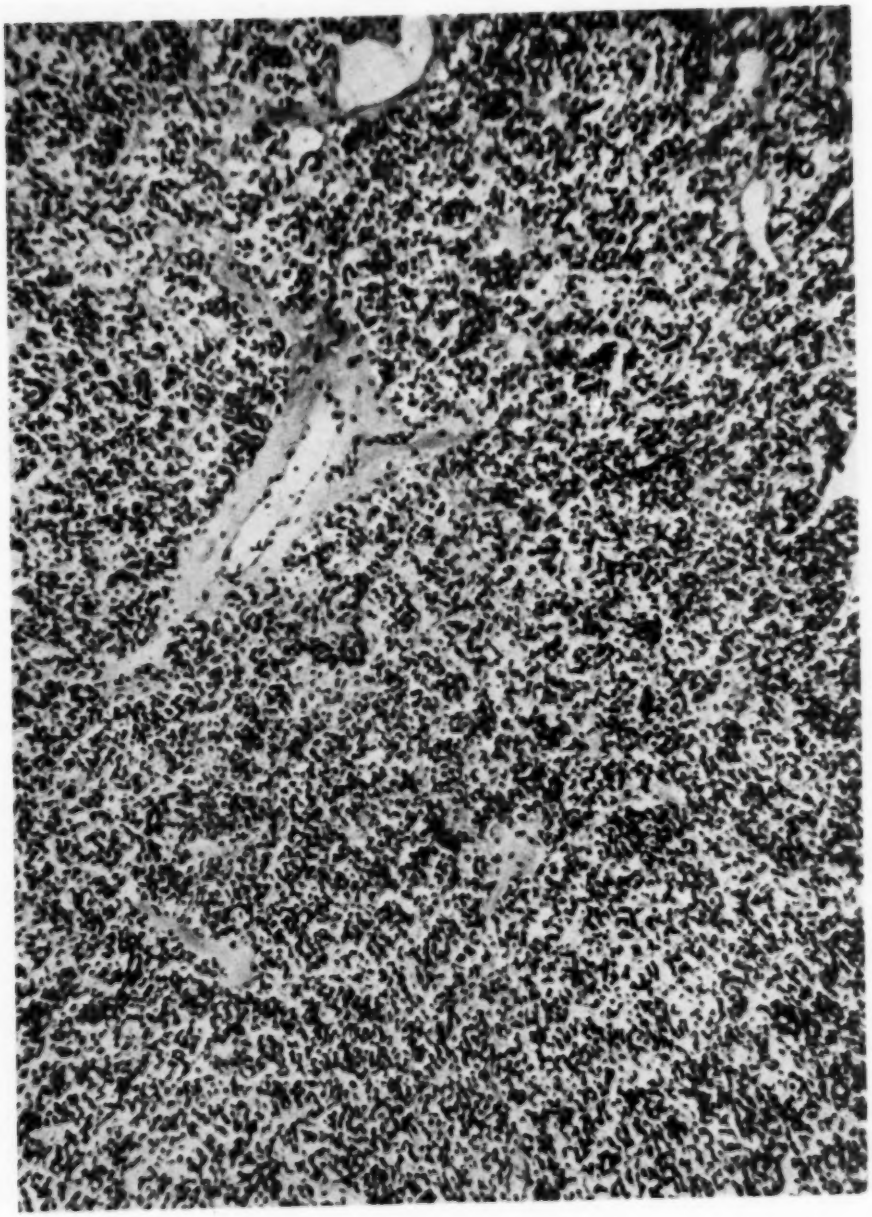

FIG. 9*a*.

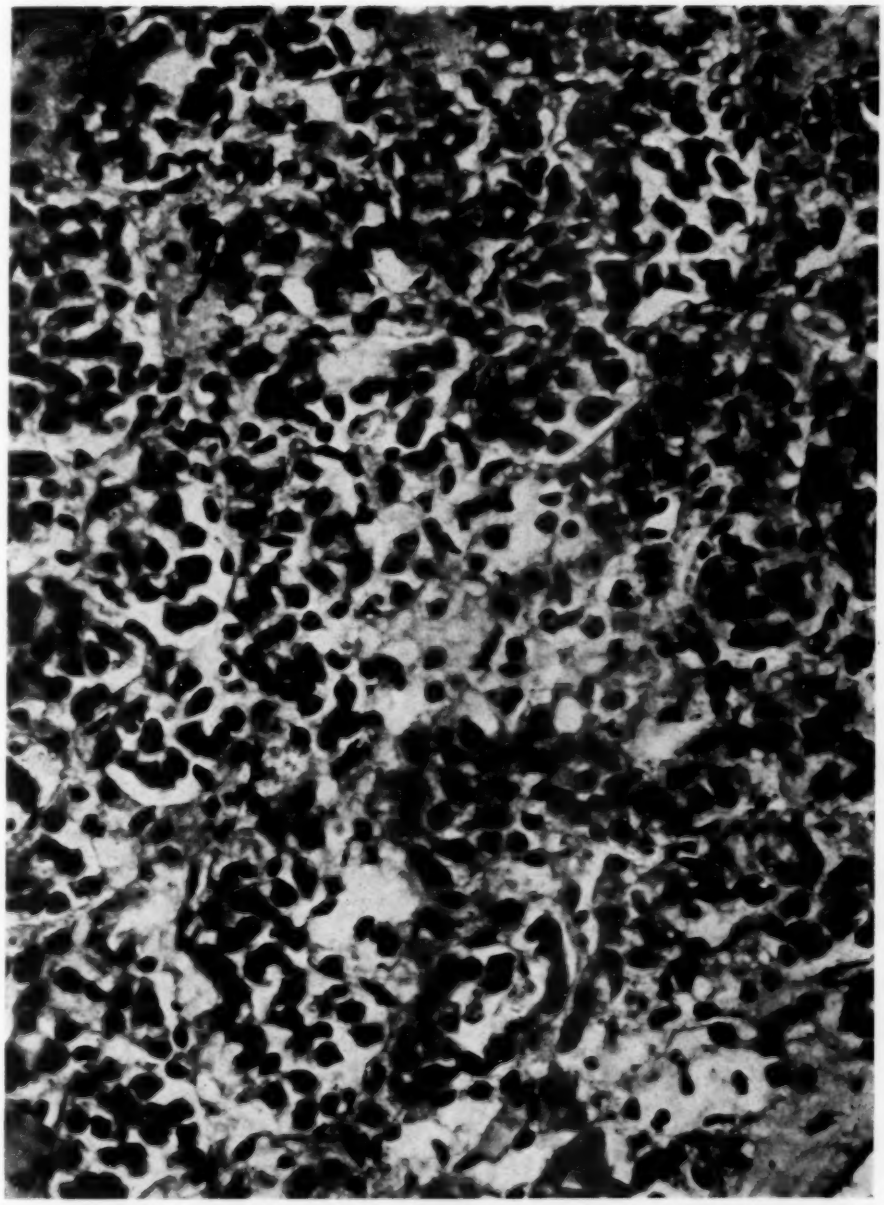

FIG. 9*b*.

FIG. 9*a* and *b*. Low power and high power views of a section of thyroid tissue from a cretinous pig, a companion to the one whose thyroid is shown in figure 8. Note the solid structures characteristic of fetal adenoma.

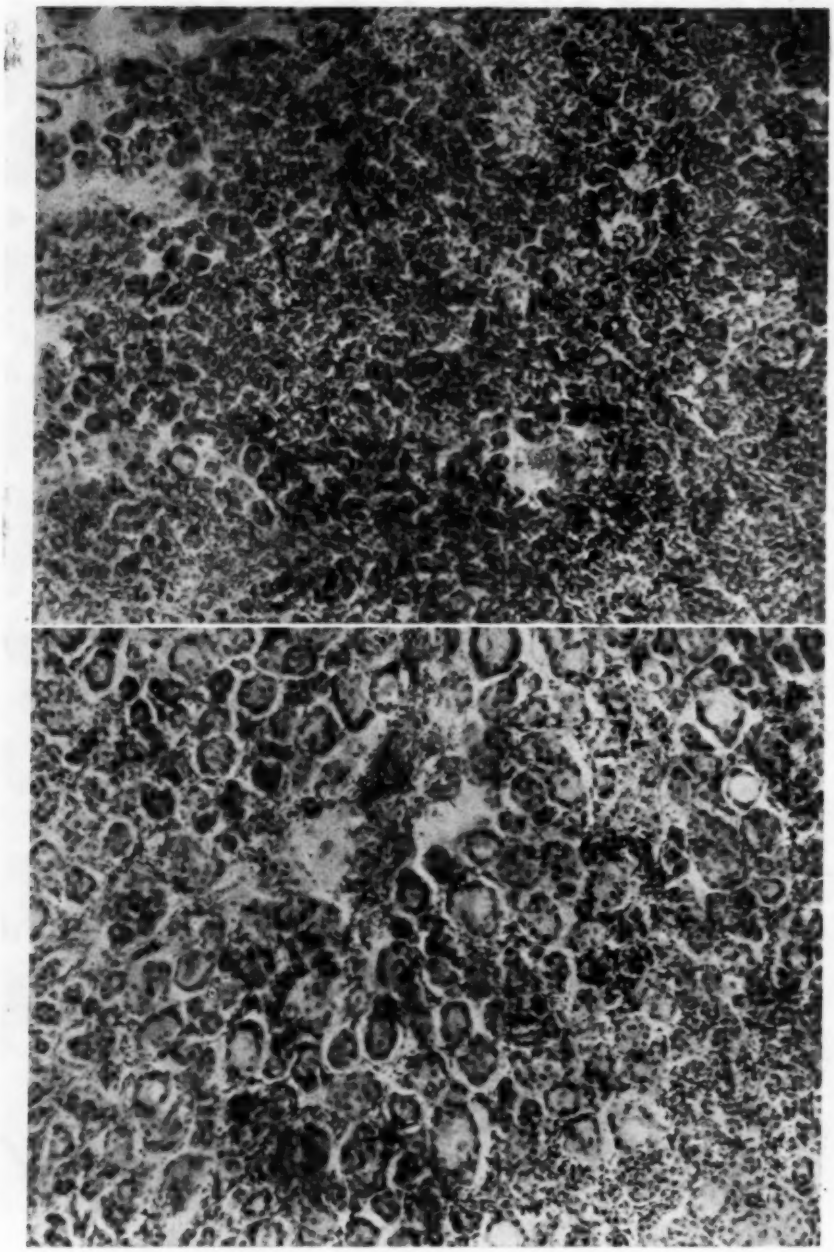

FIG. 10. Two low power views of a section of thyroid from a thyrotoxic patient who had received thiouracil for 10 months.

However, when both drugs were fed simultaneously, seven of 10 rats developed adenomata and the remaining three carcinomata of the thyroid.

The production of thyroid carcinomata under these experimental conditions raises certain practical problems relative to the dangers of using thiouracil in the treatment of hyperthyroidism. As the editorial [6] in the Journal of the American Medical Association suggests, might not the prolonged use of thiouracil in susceptible individuals lead to the development of clinical cancer of the thyroid? As yet there is no answer to this question based on experience with patients, but it certainly should cause one to be cautious in the use of thiouracil except as a preliminary medication in preparing the patient for thyroidectomy.

SUMMARY

1. Two cases of sporadic cretinism with goiter are presented together with biochemical and pathological studies.

2. Evidence for a possible relationship between hyperplasia and neoplasia of the thyroid gland is discussed.

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AN INQUIRY INTO THE INCIDENCE OF HYPERHIDROSIS IN CONVALESCENT TRENCH FOOT *

By JACOB J. SILVERMAN, Major, M.C., A.U.S., *Staten Island, N. Y.*

THE statement is sometimes made that in the later stages of trench foot one of the frequent complaints is excessive sweating of the feet. As far as can be learned from the literature no attempt has ever been made to study this phenomenon in trench foot to determine its exact incidence. Ungley and Blackwood [18] divided the clinical course of trench foot into three stages: (1) Prehyperemic stage of a few hours to several days. In this stage the feet are cold, dry, swollen, numb and discolored. (2) Hyperemic stage of six to 10 weeks. In this stage the feet are swollen, anesthetic, red and warm. Sweating is frequently absent and seems to coincide with the sensory loss. (3) Posthyperemic stage lasting from weeks to months. Raynaud-like phenomena may be found in this stage, and on exercise there is early pain and swelling. In spite of the tissue damage which may be extensive, the peripheral pulse is palpable and of good quality.[8] According to Ungley and Blackwood, in the posthyperemic stage, "there are often complaints of excess sweating or of sweat rashes; on a hot day socks are quickly soaked, but extremities may sweat heavily even when cold."

Soldiers suffering from trench foot who are evacuated to the United States are usually in the posthyperemic stage. An opportunity, therefore, presented itself at this General Hospital to study the sweat response of the feet in soldiers suffering from convalescent trench foot. Two hundred soldiers were studied and they were all from the European theater of operation. The study was limited to white soldiers whose average age was 25. The majority of the patients came from infantry units. There was an average interval of four months from the time of the onset of the condition to the date of this study. Each soldier was convalescing from either a moderate or an advanced type of trench foot. A moderate type was characterized by a typical history of exposure with skin and soft tissue changes but without evidence of gross gangrene. An advanced type was characterized by gangrene with subsequent loss of foot substance. There were 100 patients of each type in this study. For comparative purposes the sweat response was also studied in 100 patients from the general medical wards. This last group was made up of patients suffering from arthritis, malaria, valvular heart disease, hypertension, and the usual run of psychoneurosis seen on general medical wards. No patient in this last group gave a history of trench foot or symptoms from exposure to unusual cold or dampness.

* Received for publication January 16, 1946.

From the Cardiovascular Section, U. S. Army General Hospital, Camp Butner, N. C. Colonel Roy H. Turner, Surgeon General's office, arranged for this study.

Technic

To study the sweat response the technic of Silverman and Powell [12] was used. A brief description of the technic will suffice for present purposes. A 25 per cent solution of tincture of ferric chloride is applied to the sole of the foot. After drying, contact is made for a specified time on specially prepared tannic acid paper. Sweat is approximately 99 per cent water and will carry with it in solution the readily soluble ferric chloride. The tannic acid paper reacts with the soluble iron to form a stain. Prints are obtained on the paper which vary in intensity depending upon the amount of sweating. For purposes of this study, three types, depending on the degree of sweating, have been classified: (1) faint response; (2) moderate response; (3) intense response. Examples of the three types are shown (figure 1). To correlate

Type I Type II Type III

Fig. 1. Type I, faint response; Type II, moderate response; Type III, intense response. Classification used in the study of the sweat response of the sole of the foot.

the sweat response of the sole with the palm, sweat patterns of the palm and sole were taken simultaneously on the same patient. A similar technic was applied to the palm and the same classification was used (figure 2). The study was carried out by trained enlisted personnel in a quiet, comfortable room, free from distracting influences. To check the results, the tests were frequently repeated on the same patient.

Findings

Chart 1 illustrates the type of sweat response of the soles of the foot found in the three groups. A type 3, or intense response, was found in 18

Type I Type II

Type III

Fig. 2. Type I, faint response; Type II, moderate response; Type III, intense response. Classification used in the study of the sweat response of the palm.

per cent of the moderate trench foot patients, 17 per cent of the advanced trench foot patients, and 23 per cent of the general medical patients. The degree of trench foot involvement, therefore, had no bearing on the inci-

dence of excessive sweating. More interestingly, a slightly higher incidence of excessive sweating of the soles was found in the group of medical patients who gave no history of trench foot. The results of the study of the sweat response of the palm are shown in chart 2. There was an almost identical incidence of the sweat responses of the palms in the two types of trench foot. The general medical patients, however, showed a striking increase in the excessive sweat response of the palm. Whereas 36 per cent of the trench foot cases gave an intense response of the palm, 59 per cent of the general medical patients gave this same type of response.

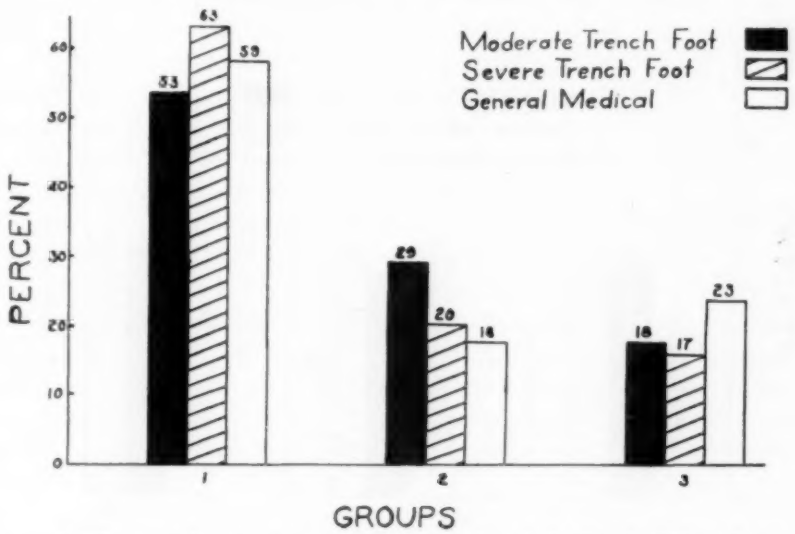

CHART 1. Comparative sweat response of the soles of the feet in 100 moderate trench foot patients, 100 severe trench foot patients, and 100 general medical patients without trench foot. Classification: 1, faint response; 2, moderate response; 3, excessive response.

Sweat patterns of the palms and soles were taken simultaneously but the figures are not shown. Of the 18 patients with moderate trench foot who gave a type 3 or intense sweat response of the sole, 14 demonstrated at the same time an intense response of the palm. There were 17 patients of the severe trench foot group with an intense sweat response of the sole, and 13 of these gave a similar sweat response of the palm. In the general medical patients, there were 23 with an intense sweating response of the soles and all these same patients simultaneously showed an intense response of the palms. In brief, where there was excessive sweating of the foot, the same type of response was almost invariably recorded for the palm, regardless of the diagnosis or degree of trench foot.

It did not follow, however, that a dry type of foot was accompanied by a dry palm. There were 53 patients with moderate trench foot who gave a type 1 or faint response of the soles, and of these only 26 gave a similar response of the palms. In the severe trench foot cases there were 63 patients

with a faint response of the soles, and of these, 60 gave a faint response of the palms. There were 59 patients in the general medical group who showed a faint response of the soles and of these, only 23 simultaneously showed a similar response of the palms. It is interesting to note, the more severe the trench foot, the higher the incidence of type 1 or faint response of the sole.

Reversing the procedure and using the palm as a guide to the type of sweating of the foot, the following figures were obtained. In the group of patients with moderate trench foot, there were 36 patients with excessive sweating of the palm, 14 of whom simultaneously showed excessive sweating

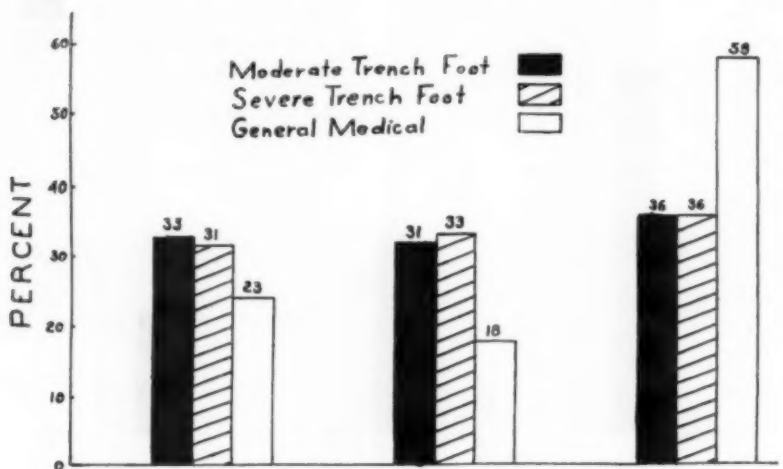

CHART 2. Comparative sweat response of the palms in 100 moderate trench foot patients, in 100 severe trench foot patients, and 100 general medical patients without trench foot. Classification: 1, faint response; 2, moderate response; 3, excessive response.

and 11 faint sweating of the soles. In the same group of patients there were 33 with a faint palmar response and of this group 26 gave a faint response of the soles. In the severe trench foot cases there were 36 patients with excessive sweating of the palms, 13 of whom gave a faint response of the soles. In this same severe group of trench foot there were 31 patients who gave a faint response of the palms and of this group, 30 gave a faint response of the soles. Studying the general medical patients, there were 59 patients who gave an excessive sweat response of the soles, while 21 showed a faint response of the soles. In this same general medical group, there were 23 patients who gave a faint response of the palm and these entire 23 simultaneously also gave a faint response of the soles. In brief, a dry palm was almost invariably accompanied by a dry sole, regardless of the type of trench foot or medical diagnosis. As the sweat of the palms increased, the sweat of the soles also increased but to a lesser degree.

Discussion

Sweating of the soles and palms is unique and differs from general body sweating on anatomic and physiologic grounds.[13] Anatomically, there are more sweat glands on the palm and sole than anywhere else on the general body surface.[7] The sweat glands on the palms and soles are arranged on ridges which assume characteristic patterns. This arrangement assures maximum grasping and tactile facility.[5] Sweating in these locations takes place continuously; whereas, on the general body surface it is intermittent.[6] Under ordinary conditions, sweating of the palms and soles is not influenced significantly by the outside temperature.[9] Increasing the outside temperature will augment general body sweating but not sweating of the palms or soles. Finally, the palms and soles reflect emotional changes.[3] In relaxed states, such as in sleep, the palms and soles are characteristically dry, regardless of the outside temperature. In states of apprehension and tension the palms and soles perspire profusely. Excessive palmar sweating seen in anxiety states is a well known clinical phenomenon.[14]

In dealing with observations on sweating, one must, therefore, be careful to differentiate sweating of the palms and soles from general body sweating. It should be emphasized, the observations in this study were confined to the palms and soles. Preliminary studies of general body sweating in the trench foot patients were also carried out.* The trench foot patients, together with controls, were placed in an experimental environment in which the temperature was gradually raised. As the temperature was raised, sweating increased generally over the entire body, except for the soles and palms. The dorsum of the feet and hands shared equally in the increased sweating. Exercise caused a similar response. No significant difference of excessive sweating of the general body was found between the trench foot patients and the controls.

It may logically be asked why the palms and soles failed to give identical responses in all patients. Normally, sweating of the soles and palms behaves as a similar mechanism; quantitatively, however, there is a significant difference. Careful measurements have shown that the rate of water loss in the toetips is approximately one-half to two-thirds that in the fingertips.[2, 11] With slight sweating of the palms this difference is not noticeable. The difference becomes more apparent as the stimulus for this type of sweating is increased and can be demonstrated by the technic used in this study.

Cold causes an inhibition of sweating both locally and reflexly. A variety of pathologic changes has been described in trench foot.[4] The skin, being the most exposed organ, is one of the first to react to cold. Most of the observations, however, have been confined to blood vessels, nerves, muscles, and connective tissue beneath the skin. Degenerative changes in the sweat glands have been noted. More important, perhaps, from a sweating standpoint, are the changes seen in the nerve endings.[1, 4] Sweat-

* A recently described colorimetric technic [15] was used to record this type of sweating.

ing behaves as a cholinergic mechanism; on anatomic grounds, however, the sweat fibers travel along a sympathetic pathway and are contained in the peripheral nerves. Severance or destruction of this pathway leaves the innervated part anhydrotic. Clinically, the early symptoms of nerve involvement in trench foot are striking.[17] At first there is an uncomfortable sensation of coldness followed by numbness. There may be some paresthesias and vague aches and pains in the arches and ankles. The patients frequently complain of clumsiness and describe their sensations as "walking on blocks of wood." The feet may be anesthetic to pain, touch, and temperature. There is anhidrosis and this follows rather closely the disturbance in sensation. As improvement occurs, one of the early signs observed is a return of the sweating.[18] The return of the sweating function will depend to a great degree on the recovery of the damaged nerve endings. If any changes in the sweat mechanism are to be predicted in severe trench foot, a picture of relative anhidrosis rather than hyperhidrosis should be expected.

In a recent study of the casualties of the Attu campaign, Lesser [10] pointed out that the status of the vasomotor disturbances frequently seen in immersion foot (a condition closely allied to trench foot) is indefinite and difficult to evaluate. In Lesser's series there were two groups of patients. The first group presented severe gangrene and loss of foot substance. Excessive sweating was not a feature in this group; these patients seemed to show few signs and symptoms of a vasomotor imbalance. The second group, those without tissue loss, presumably the milder cases, was characterized by a high incidence of vasomotor imbalance. These milder cases complained of coldness and excessive sweating of the feet. Repeated lumbar sympathetic novocaine blocks in this second group gave disappointing results. Lesser felt that the difference in the two groups may be related to a "constitutional sympathetic nervous system instability of the individual patients."

The milder trench foot patients, those without gangrene or tissue loss, formed by far the largest group evacuated to general hospitals in the United States. The complaints of many of these patients were often entirely out of proportion to the findings on examination. Trench foot, like any other somatic disorder, has psychogenic components which may modify and color the underlying condition. It is generally agreed that, given the necessary conditions of coldness, dampness, immobility, fatigue, improper hygiene and lack of proper footgear, trench foot can occur in any soldier. Moreover, in trench foot, the anxiety state may be one of the predisposing factors in its development. One of the cardinal principles in the prevention of trench foot is the matter of keeping the feet dry. However, in severe anxiety states, it is practically impossible to keep the feet dry, for like palmar sweating, it is continuous and excessive. It is interesting to note that in many of our patients with trench foot we have been able to elicit a history indicating a high incidence of excessive sweating of the palms and soles, even before induction.

As stated above, sweating of the palms and soles is continuous and occurs normally. The average patient is not aware of this phenomenon and particularly is not observant as to the amount of sweating. With the development of trench foot, however, any sign or symptom relating to the foot takes on added significance. A soldier returning with a diagnosis of trench foot may be unusually apprehensive, not only about his feet but also about many other problems. He hears all kinds of rumors. Naturally, he is concerned when he hears that trench foot leads to loss of toe or limb. Excessive sweating in such a patient should not be unusual. Furthermore, many of these patients have been harboring fungous conditions of their toes and feet. "Athlete's foot" and excessive sweating are frequently seen together and both tend to aggravate each other. It is surprising how many patients attribute both conditions to trench foot.

As Scoville [19] pointed out, trench foot, like low back pain, is a condition which easily lends itself to the development of a neurosis. The onset is dramatic, and the complaints, especially in the milder cases, are difficult to evaluate. The medical officer at first had little or no experience with trench foot. The emphasis was on conservatism and hospitalization was often prolonged. It was easy, therefore, for many patients to capitalize on the situation. Furthermore, the diagnosis of trench foot has an emotional appeal which is socially acceptable to the neurotic. Trench foot is a mark of a fighting soldier. Many a severe anxiety problem has been evacuated to the United States camouflaged under a diagnosis of trench foot.

That the excessive sweating of the feet seen in patients with trench foot is not purely a local manifestation but part of a generalized process is attested by the following facts. Patients with unilateral involvement showed no higher incidence of hyperhidrosis in the affected extremity than in the uninvolved extremity.[16] Secondly, the severity of trench foot had no bearing on the incidence of hyperhidrosis. In fact, those with the severer type of trench foot had, if anything a tendency toward a drier foot. Furthermore, when the trench foot patients were compared with the general medical patients, a slightly higher incidence of hyperhidrosis was found in the latter group, particularly those with functional complaints. Finally, in those patients who complained of excessive sweating of the feet, invariably there was excessive sweating of the palm and often of the axillae. These are the locations for emotional sweating. Where there was a dry palm there was practically always a dry foot, regardless of the type of trench foot or medical diagnosis.

Summary

1. An attempt was made to study the incidence of hyperhidrosis in 200 patients convalescing from varying degrees of trench foot, and the findings were compared with 100 general medical patients without trench foot. The degree of trench foot seemed to have no bearing on the incidence of

hyperhidrosis. The general medical patients showed a slightly increased incidence of hyperhidrosis.

2. The hyperhidrosis seen in trench foot is part of a generalized process similar to that seen in an anxiety state.

3. Hyperhidrosis is not a diagnostic feature of convalescent trench foot. In a patient convalescing from trench foot the complaint of excessive sweating of the feet should invite investigation for other causes of hyperhidrosis.

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ON THE TOXICITY OF THE MERCURIAL DIURETICS: OBSERVATIONS ON EIGHTEEN CASES WITH SUGGESTIONS FOR THE PREVENTION OF TOXIC REACTIONS *

By Solomon Ben-Asher, M.D., *Jersey City, N. J.*

Since the introduction of novarsurol as a diuretic by Saxl and Heilig [1] in 1923, dehydration by means of the mercurial has played an important rôle in the treatment of congestive heart failure. Within recent years, however, instances of fatal and non-fatal reactions have been described in the literature. These reactions, though they occur infrequently, cause a great deal of apprehension when one has to resort to the use of the drug.

The literature on the toxic reactions to the mercurial diuretics published prior to 1942 has been adequately reviewed by DeGraff and Nadler.[2] In 1944, Wexler and Ellis [3] reported two more cases with fatal and nine cases with non-fatal reactions. The following year, Volini, Levitt, and Martin [4] described three instances of sudden death following mercurial diuresis. Another fatality was also reported in the same year by the author.[5]

In spite of the increasing number of clinical reports and the abundant experiments on animals, the explanations for these toxic effects are as yet speculative. The literature indicates widely varying opinions concerning their mechanism. Observations, either clinical or laboratory, should be of value in elucidating their pathogenesis and thus establishing a firmer basis for the therapy of congestive heart failure.

The purpose of this report is to record observations on the toxicity of the mercurial diuretics in 18 patients in the hope that these observations may throw further light on the mechanism of the reactions as well as on the methods of their prevention.

General Considerations

Incidence. Considering the extensive use of the mercurial diuretics, the number of serious reactions reported from their use is very small. DeGraff and Nadler [2] state that approximately 6000 injections of mercupurin have been given each year in Bellevue Hospital since 1934, with no serious toxic reactions or deaths that may be attributed to the drug. The two fatal cases reported by Wexler and Ellis [3] occurred in a series of 5,200 injections during a six-month period. The 18 cases comprising this report occurred in a five-year period. The number of injections during this period can not be determined.

* Received for publication December 14, 1945.
From the medical departments of the Medical Center, the Fairmount Hospital, and the Greenville Hospital, Jersey City.

Although statistical data are not available, the frequency of mild reactions is probably greater than that of fatal reactions. In general, it can be stated that the incidence of toxic reactions following the mercurial diuretics is probably lower than that of other drugs used with equal frequency.

Pathogenesis. There are a number of theories to explain the mechanism of these reactions. The fact that some fatalities occurred in cases in which previous injections did not produce any reactions has led Greenwold and Jacobson [6] to consider them as anaphylactic in nature. The previous injections, they believe, might have sensitized the patient to the mercury ion. This theory, however, does not explain the fatalities that have occurred after the first injection.

Another explanation for the toxic manifestations is that it is due to a direct action of the mercurial diuretic on the heart muscle. This theory receives support from some laboratory and clinical evidence. Salant and Kleitman [7] were the first to observe ventricular fibrillation in normal dogs following the intravenous administration of inorganic mercurial salts. Later Jackson [8] demonstrated that fibrillation and death could be produced in normal dogs by the intravenous injections of 5 c.c. of a 2 per cent solution of salyrgan. Chastain and Mackie [9] also showed that esidrone injected intravenously in normal dogs will produce changes in the electrocardiogram followed by ventricular flutter, fibrillation and death. By injecting normal dogs with various mercurial compounds, Barker, Lindberg and Thomas [10] obtained changes in the T-waves, runs of extrasystoles, ventricular tachycardia, ventricular fibrillation and death. In two of the fatal cases described by Volini, Levitt, and Martin,[4] the electrocardiogram showed the development of ventricular fibrillation. In one case there were changes in the ST junction, the ST interval, and also in the T-waves. The electrocardiogram in a non-fatal case described in this report showed changes in the ST segment followed by ventricular premature systoles and ventricular paroxysmal tachycardia. There was normal sinus rhythm when the patient recovered. We thus have evidence in both the experimental animal and in man that the reaction may be due to a direct effect of the drug on the heart muscle.

Hyman [11] believes that the reactions are due to technical rather than hemodynamic factors. The reactions, he states, resemble the syndrome of speed shock in which the blood is rendered non-coagulable when any material is rapidly injected intravenously. From a study on the influence of velocity on the response to intravenous injections, Hirshfeld, Hyman and Wanger [12] state that solutions with larger molecules should be given more slowly than solutions with smaller molecules, and that toxic substances should be given intermittently as well as slowly.

Toxic reactions may also occur as a result of a disturbance in the water and electrolyte equilibrium of the body induced by the mercurial diuretics. Soon after their introduction of novarsurol as a diuretic, Saxl and Heilig [1] showed that diuresis is accompanied by an absolute increase in the chlorides of the urine. Later Crawford and McIntosch [13] found that the increase in

the chloride excretion in the urine is accompanied by a fall in the serum chloride. Blumgart and his co-workers [14] demonstrated that diuresis is accompanied by an increased secretion of chloride, sodium and potassium. The amount of chloride in the extra urine excreted is greater than that of an equal volume of body fluid. This increased secretion of inorganic ions is accomplished by a relative decrease in tubular reabsorption, the rate of glomerular filtration remaining unaffected. Diuresis is also accompanied by a decrease in the serum chloride concentration which, they believe, is a consequence of the excess urinary chloride loss, and by an approximately equivalent rise in the serum bicarbonate concentration. The serum concentration of sodium and calcium is unchanged.

Chabanier, Lebert, and Lumiere,[15] however, found a drop in the blood sodium and chloride. Keith, Barrier, and Whelan [16] also found increased secretion of sodium following novarsurol in cases of nephritis with edema. The changes in the concentration of the inorganic ions of the blood were inconstant and never marked in degree.[17] Poll and Stern [18] reported seven cases exhibiting toxic reactions to mercurial diuretics which, they believe, were due to a loss of sodium similar to the acute collapse seen in Addison's disease. These inconstant and conflicting findings may be explained by the fact that whereas the mercurial diuretics produce a decrease in tubular reabsorption with no change in glomerular filtration, dehydration produces the opposite effect; i.e., an increased tubular reabsorption and a decrease in glomerular filtration.[19] Hence, the results may vary in different cases and in the same patient at different times.

Lyons and his associates [20] have shown that dehydration is accompanied by a fall in the plasma volume associated with a fall in venous pressure and pulse pressure. Coincident with the fall in the plasma volume there is an increase in the serum protein and a rise in the hematocrit reading. As a result of marked hemoconcentration, vascular collapse and death may follow because of a diminished return flow to the heart and a fall in the cardiac output.

Lastly, digitalis toxicity may occur following the administration of the mercurial diuretics as a result of the mobilization of digitalis from the retained tissue fluids. However, this is seldom serious and disappears spontaneously after the cessation of digitalis.

Clinical Manifestations. The reactions may be fatal and non-fatal. Wexler and Ellis [3] have divided the non-fatal cases into immediate and delayed types. The immediate fatal and non-fatal reactions are characterized by dyspnea, cyanosis or pallor, irregular breathing, drop in blood pressure, cardiac irregularity, unconsciousness and convulsions. Cardiac arrest may occur before respiratory paralysis within five minutes after the injection. Mild non-fatal immediate reactions may be manifested by a sense of apprehension, substernal discomfort, transient dyspnea, orthopnea, cyanosis, sweating and tachycardia. Delayed reactions occur one to two hours after the injection with symptoms of asthma or pulmonary edema. Reactions

may also occur six to 12 hours later with symptoms of weakness, apathy, mental confusion, delirium, coma and death. Hypersensitiveness may present itself with symptoms of fever, erythema, paresthesia and ulcerative stomatitis.

Prevention of Reactions. It is generally stated that there is no known way of avoiding a reaction. The presence of kidney disease is considered a contraindication to the use of the mercurial diuretics, although one may have to resort to their use in spite of impaired kidney function. From experiments on cats, DeGraff and Lehman [21] conclude that toxic reactions cannot be avoided by dilution of the drug nor by slow injection. Hyman,[11] on the other hand, believes that reactions can be prevented by intermittent injections. Barker, Lindberg and Thomas [10] emphasize caution in the intravenous use of the mercurial in a water-logged patient.

It will be apparent from the discussion below that the mercurial diuretics should not be given during a high environmental temperature. Reactions may also be prevented by slow intermittent injections. In one case reactions were prevented by the preliminary injection of sodium thiosulfate.

Clinical Material

The material dealt with in this report has been assembled from three hospitals and comprises 18 cases in which toxic reactions occurred following the intravenous injection of the mercurial diuretics. In no case was there any evidence of impaired kidney function. In 17 cases the reactions were not fatal; in one it was fatal. The latter case, reported elsewhere in detail,[5] was associated with a high environmental temperature and high humidity. Evidence was presented indicating that the abnormal environmental conditions, causing an increase in the loss of inorganic ions through the sweat glands, were a contributing factor in the cause of death.

In order to determine whether or not there was any correlation between environmental conditions and the toxic reactions in the non-fatal cases, the temperature and humidity at the time of the injections were determined from the United States Weather Bureau. The data as well as other observations will be presented chiefly in tabular form, supplemented by brief summaries of the records of a few illustrative cases.

Case Reports

Case 10. R. H., a 48-year-old man, was admitted to the Fairmount Hospital on March 23, 1943, complaining of dyspnea, orthopnea, cough and swelling of the lower extremities. A known cardiac for the past 18 years, he felt well until 15 months before admission, at which time he began to notice swelling of the ankles and shortness of breath. He had been on a maintenance dose of 0.1 gm. of digitalis and had received four injections of mercupurin and one mercurin suppository before entry without any untoward effect. The last injection was given three weeks before admission to the hospital.

Physical examination revealed peripheral edema, ascites, enlarged liver and distended veins of the neck. The heart was enlarged. The second pulmonic sound was

accentuated. Systolic and diastolic murmurs were heard over the mitral area. The rhythm was totally irregular; the ventricular rate was 108; the radial pulse was 90. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The urine showed a trace of albumin, no sugar, an occasional white cell, and no red cells. The blood count was normal. A chest film showed an enlarged heart with mitral configuration. An electrocardiogram showed auricular fibrillation and right axis deviation. The diagnosis was rheumatic heart disease, mitral stenosis, mitral regurgitation, enlarged heart, auricular fibrillation and congestive heart failure.

Under rest and 0.1 gm. of digitalis daily he improved but the edema persisted. On the third day after admission, the patient was given intravenously 2 c.c. of mercupurin. About two minutes later he became pale, sat up in bed and complained of marked palpitation. The respirations became labored and the ventricular rate increased to 168, the pulse rate to 144. The blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. The reaction lasted about three minutes and the patient recovered spontaneously. A diuretic response of 3500 c.c. resulted.

The peripheral edema, however, returned and it was found necessary again to resort to mercupurin. The patient refused any but the intravenous method. After an interval of 10 days, 2 c.c. of mercupurin were given slowly and intermittently at a rate of 0.1 c.c. every 15 seconds. There was no reaction after the injection. Four subsequent injections given with the same technic produced no untoward effects. He died of congestive failure eight weeks after the reaction.

Case 16. M. F., a 62-year-old female, entered the Medical Center on July 9, 1944, because of palpitation, dyspnea and peripheral edema of six months' duration. She had been on a maintenance dose of 0.1 gm. of digitalis and received eight injections of mercupurin without any untoward results.

Physical examination revealed peripheral edema, ascites, enlargement of the liver and distended veins of the neck. The heart was enlarged to the left. A systolic thrill was felt over the aortic area. The second aortic sound was absent. A loud rough systolic murmur was heard over the aortic area and a soft diastolic murmur over the left sternal border. There was a small Corrigan pulse. The blood pressure was 140 mm. Hg systolic and 60 mm. diastolic. The Wassermann reaction was negative. The urine showed a trace of albumin, a trace of sugar and a specific gravity of 1.022. The blood count showed 4,260,000 red cells and 7,200 white cells. The differential count was normal. The non-protein nitrogen was 38 mg., sugar 126 mg. per 100 c.c. of blood. An electrocardiogram showed a regular sinus rhythm, depressed ST_1 and ST_2, and left axis deviation. Roentgen examination revealed cardiac enlargement, moderate widening of the aorta, with dancing aortic calcifications. The diagnosis was etiology unknown, calcific aortic stenosis, aortic insufficiency, enlarged heart, regular sinus rhythm and congestive heart failure.

She improved under rest, digitalis, and limitation of fluids. Mercupurin was given first once a week and later once in two weeks. The environmental temperature during the entire period between August 10 to August 17 was exceedingly high, the daily maximum temperature ranging from 92° F. to 96° F. She was given 2 c.c. of mercupurin intravenously on August 15. The maximum environmental temperature for that day was 93° F., and the relative humidity varied from 88 per cent to 69 per cent. Six hours after the injection she became restless and was mentally confused. The next day she became more irrational. The skin and tongue were dry. The maximum temperature on that day was 93° F., and the relative humidity ranged from 88 per cent to 98 per cent. She was given salts and fluids were forced. The third day after injection she was still confused and irrational. The temperature on that day again reached a maximum of 93° F., and the relative humidity ranged from 91 per cent to 76 per cent. The same day the non-protein nitrogen was 50 mg., sugar 136 mg., chloride 446.9 mg. per 100 c.c. of blood. The total protein was 9.8 gm. The

carbon dioxide was 55 vol. per cent. The fifth day after injection the symptoms disappeared. The non-protein nitrogen on August 24 was 42 mg., sugar 128 mg., chloride 640 mg. per 100 c.c. of blood. The carbon dioxide was 60 vol. per cent. There were no untoward effects after the subsequent 18 injections. She left the hospital improved 10 months after her admission.

Case 17. B. D., a 53-year-old female, entered the Greenville Hospital on February 23, 1945, because of dyspnea and increasing edema of one year's duration. She gave a history of rheumatic fever at the age of 16. Mercupurin was injected six times before entry; the last injection was given two weeks before entry.

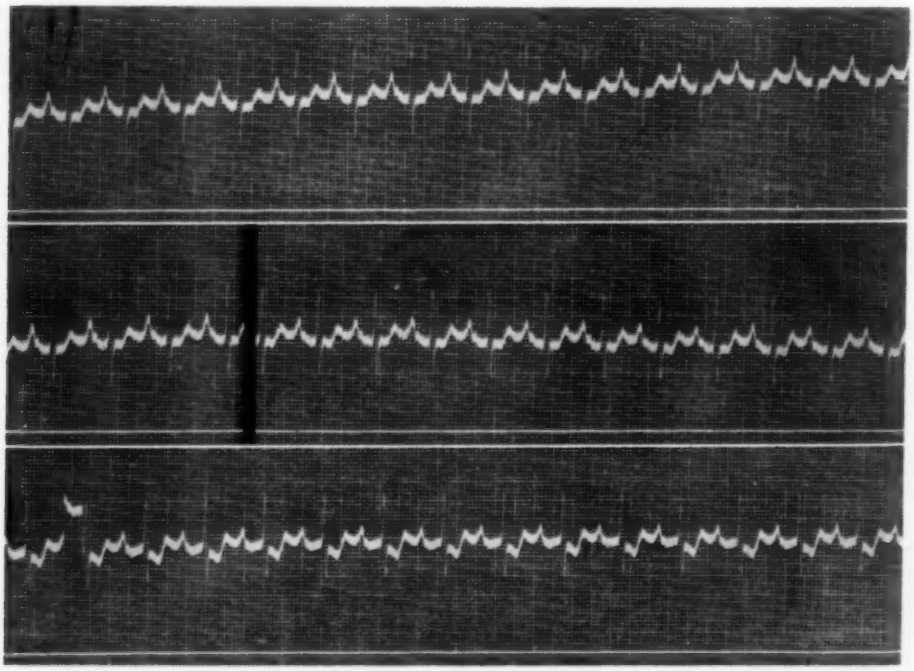

FIG. 1. (*Case 17*). Three portions of the long strip of Lead II, showing alterations in the P-wave, ST segment and the T-wave after injection of mercupurin intravenously. The black line indicates the time of injection. Described in text.

Physical examination revealed distended veins of the neck, peripheral edema, ascites, enlarged liver and congestive râles in both lungs. The heart was enlarged to the left. A systolic thrill was felt over the aortic area. Systolic and diastolic murmurs were heard at the base and apex. The rhythm was regular. There was a small Corrigan pulse. The blood pressure was 210 mm. Hg systolic and 90 mm. diastolic. The urine showed a specific gravity of 1.024, no albumin and no sugar. The blood count was normal. The Wassermann reaction was negative. A roentgenogram of the chest revealed an enlarged heart with mitral configuration and pronounced hypertrophy of the left ventricle. An electrocardiogram showed a regular sinus rhythm, deep S_1, S_2, and slightly sagging ST_1, ST_2. The P wave was 4½ mm. The PR interval was 0.24 second. The diagnosis was rheumatic heart disease, hypertensive heart disease, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency, enlarged heart, regular sinus rhythm, partial heart block (prolonged P–R interval) and congestive heart failure.

An intravenous injection of mercupurin was given slowly on the second day of admission. About two minutes later, the patient complained of substernal distress and sat up in bed. The face became pale, the respirations labored and the pulse rapid and irregular. The episode lasted from two to three minutes. A good diuretic effect was obtained, and the patient improved. The edema, however, returned, and it was found necessary to repeat the mercupurin. Since the patient refused any but the intravenous method, that route was again resorted to. An electrocardiogram was taken before the injection; the camera of the machine was shut off just before the insertion of the needle into the vein and the solution was injected slowly but not intermittently with the patient connected to Lead II. A continuous tracing was then

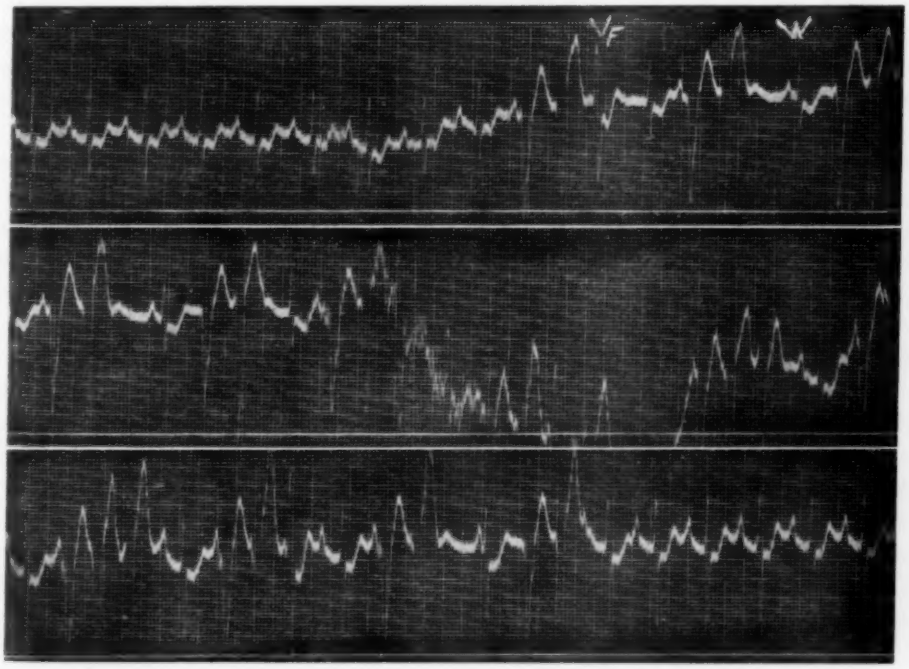

FIG. 2. Continuous tracing of the last strip of figure 1, showing premature ventricular systoles and paroxysmal ventricular tachycardia. V_F is a ventricular fusion beat. At W, the P–R interval is only .16 second. The A–V junctional tissue has recovered from its relative refractory phase; this is similar to the Wenckebach phenomenon.

obtained in that lead. A reaction similar to that obtained after the previous injection took place 2.6 seconds later. This reaction lasted 2.2 minutes, after which the patient felt better.

Figure 1 shows Lead II before and after the injection. The black line indicates the time of the injection. Figure 2 shows the various later changes in the electrocardiogram after the injection. The first tracing in figure 1 shows a P-wave of 4½ mm., a deep S_2, slightly sagging ST_2 and a PR interval of 0.24 second. In the last tracing of figure 1 and in the first portion of the upper tracing in figure 2, the P-wave is only 3 mm.; the ST segment is depressed 2 mm.; T_2 is diphasic. These changes are followed by ventricular premature systoles and later by paroxysmal ventricular tachycardia. The episode lasted 2.2 seconds, after which there was normal sinus rhythm. The ST segment remained depressed, but T_2 became positive.

The following week, the mercupurin, administered slowly but not intermittently, was preceded by 1 gm. of sodium thiosulfate intravenously. There was no reaction after the injection. There were no changes in the electrocardiogram. Two subsequent similar procedures gave the same results. The patient died of cerebral hemorrhage six weeks after the reaction.

Discussion

An analysis of the accompanying table reveals two types of reactions. In the first type, the reaction occurred six to 12 hours after the injection and was characterized by weakness, drowsiness, mental confusion, apathy, restlessness, and in one instance by coma and death. This type comprised 10 cases, eight of which had hypertensive and arteriosclerotic heart disease. One had calcific aortic stenosis and one rheumatic heart disease. The ages ranged from 53 to 71 years. Of the 10 patients, five received ammonium chloride; six patients had previous injections of the mercurial diuretics. In nine instances the mercurials were given under abnormal environmental conditions; the temperature ranged from 91° F. to 99° F., and the relative humidity from 36 per cent to 93 per cent. In one instance, case 12, the maximum temperature was 87° F. and the relative humidity ranged from 36 per cent to 77 per cent. Nine patients recovered with the administration of salt and water. Three of the patients who recovered died eight months to two years later of the usual complications of cardiovascular diseases.

Eichhorst [22] in 1898 was the first to note somnolence, disorientation, delirium and apathy following diuresis with digitalis and theobromine sodiosalicylate. Srnetz [23] in 1934 noted somnolence and mental confusion following diuresis with salyrgan. Poll and Stern [18] in 1936 described seven cases with similar untoward effects following mercurial diuresis. Three of their patients developed coma and died. These reactions, they believe, were caused by the loss of sodium, resulting from the depletion of sodium chloride reserves of the body.

The reactions in the group described in this report were evidently caused by a disturbance in the water and electrolyte balance in the body resulting from two factors. One factor is the loss of inorganic ions produced by the mercurial diuretics; the other is the loss through the sweat glands as a result of abnormal environmental conditions.

In the second type, the reaction occurred immediately after the injection and was characterized by pallor, cyanosis, substernal distress, palpitation, dyspnea, orthopnea, tachycardia, irregular rhythm, and a fall in blood pressure. The injections were given slowly. The reaction occurred about two to three minutes after the injection, and lasted about two to five minutes. This was noted in eight cases, five of which had rheumatic heart disease, two had hypertensive and arteriosclerotic heart disease, and in one the etiology was unknown. The ages ranged from 35 to 66 years. All patients were in severe congestive failure and had had previous injections of mercupurin. In seven cases the reaction did not occur on subsequent injections when given intermittently.

TABLE I

Toxic Reactions to the Mercurial Diuretics

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
1	M.L.	63	Aug. 21, 1939	Hypertension, arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	+++	Yes	6 gm. per day for 3 days.	Salyrgan 2 c.c.	None	10 hours	91° F. 93% to 78%.	Weakness, drowsiness, disorientation, stupor.	Recovered with salt and water; died of acute myocardial infarction 24 months after reaction.
2	K.S.	42	Mar. 20, 1940	Rheumatic fever, enlarged heart, mitral stenosis, mitral insufficiency, auricular fibrillation.	++++	Yes	6 gm. per day for 3 days.	Salyrgan 2 c.c.	5	2 minutes	37° F. 55% to 61%.	Cyanosis, palpitation, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 1½ months after reaction.
3	J.L.	71	July 27, 1940	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++	Yes	No	Mercupurin 2 c.c.	2	8 hours	99° F. 55% to 61%.	Apathy, drowsiness, stupor, oliguria.	Recovered with salt and water; died of cerebral hemorrhage 16 months after reaction.
4	F.B.	66	May 14, 1941	Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis, myocardial fibrosis, auricular fibrillation.	+++	No	No	Mercupurin 2 c.c.	5	2 minutes	71° F. 58% to 39%.	Palpitation, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 2 months after reaction.
5	S.R.	53	June 22, 1941	Hypertension, enlarged heart, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercupurin 2 c.c.	None	12 hours	94° F. 63% to 40%.	Weakness, restlessness, mental confusion, stupor.	Recovered with salt and water; died of myocardial infarction 1 year after reaction.

TABLE I—*Continued*

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
6	L.K.	62	Aug. 9, 1941	Hypertension, arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, auricular fibrillation.	++	Yes	No	Mercupurin 2 c.c.	None	10 hours	92° F. 73% to 37%.	Drowsiness, weakness, mental confusion.	Recovered with salt and water. In severe congestive failure at this date.
7	B.C.	40	Mar. 18, 1942	Unknown, enlarged heart, auricular fibrillation.	++++	Yes	6 gm. per day for 3 days.	Mercupurin 2 c.c.	6	2 minutes	58° F. 60% to 40%.	Pallor, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 1½ months after reaction.
8	M.S.	64	July 20, 1942	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	+++	No	No	Mercupurin 2 c.c.	2	12 hours	93° F. 67% to 44%.	Restlessness, mental confusion, delirium.	Recovered with salt and water. Condition unchanged at this date.
9	S.K.	58	Feb. 19, 1943	Hypertension, arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++++	Yes	No	Mercupurin 2 c.c.	4	3 minutes	48° F. 42% to 38%.	Pallor, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 1½ months after reaction.
10	R.H.	48	Mar. 25, 1943	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++++	Yes	No	Mercupurin 2 c.c.	4	2 minutes	63° F. 56% to 29%.	Pallor, palpitation, dyspnea, orthopnea, tachycardia, fall in blood pressure.	No reaction when the injection was given intermittently. Died of congestive failure 2 months after reaction.

TABLE I—*Continued*

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
11	M.B.	45	June 25, 1943	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++	Yes	No	Mercupurin 2 c.c.	92	12 hours	96° F. 84% to 36%.	Stupor, coma, and death.	
12	W.H.	62	Aug. 1, 1943	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++++	Yes	6 gm. per day for 3 days.	Mercupurin 2 c.c.	None	10 hours	87° F. 77% to 36%.	Weakness, delirium, mental confusion.	Recovered with salt and water; condition unchanged at this date.
13	F.K.	55	Aug. 2, 1943	Hypertension, enlarged heart, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercupurin 2 c.c.	3	11 hours	91° F. 71% to 60%.	Weakness, delirium, restlessness, dry tongue.	Recovered with salt and water; condition improved at this date.
14	F.H.	41	May 14, 1944	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	++++	Yes	No	Mercupurin 2 c.c.	7	3 minutes	78° F. 44% to 87%.	Palpitation, cyanosis, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. Died suddenly 2½ months after reaction.
15	J.L.	60	July 8, 1944	Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis, myocardial fibrosis, regular sinus rhythm.	++	Yes	6 gm. per day for 3 days.	Mercupurin 2 c.c.	None	8 hours	92° F. 78% to 39%.	Restlessness, mental confusion.	Recovered with salt and water; condition unchanged at this date.

TABLE I—*Continued*

No.	Case	Age	Date	Diagnosis	Degree of Failure	Digitalis	Ammonium Chloride	Diuretic and Amt.	No. of Previous Injections	Interval Between Injection and Reaction	Environmental Temp. and Humidity	Reaction	Comments
16	M.M.	62	Aug. 15, 1944	Unknown, calcific aortic stenosis, aortic insufficiency, enlarged heart, regular sinus rhythm.	++++	Yes	No	Mercupurin 2 c.c.	8	6 hours	93° F. 88% to 69%.	Weakness, restlessness, mental confusion, delirium, dry skin, dry tongue.	Recovered with salt and water; condition improved at this date.
17	B.D.	53	Feb. 25, 1945	Rheumatic fever, aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency, enlarged heart, partial heart block (prolonged P.R. interval), regular sinus rhythm.	+++	Yes	No	Mercupurin 2 c.c.	6	2.2 minutes	48° F. 59% to 49%.	Substernal distress, pallor, dyspnea, orthopnea, paroxysmal ventricular tachycardia.	No reaction when a preliminary injection of 1 gm. of sodium thiosulfate intravenously was given. Died of cerebral hemorrhage 1½ months after reaction.
18	A.M.	35	June 17, 1945	Rheumatic fever, mitral stenosis, mitral insufficiency, enlarged heart, auricular fibrillation.	+++	Yes	4 gm. per day for 3 days.	Mercupurin 2 c.c.	5	2 minutes	91° F. 78% to 66%.	Cyanosis, palpitation, dyspnea, orthopnea, tachycardia.	No reaction when the injection was given intermittently. In severe congestive failure at this date.

Case 17 deserves special attention. An electrocardiogram taken during the reaction showed changes in the P-wave, ST segment and the T-wave, followed by ventricular premature systoles and paroxysmal ventricular tachycardia. The patient recovered, and the electrocardiogram returned to normal sinus rhythm. Reactions did not occur after subsequent injections when they were preceded by sodium thiosulfate intravenously. The use of this drug to prevent a reaction suggested itself following the work of Johnston [24] who showed that an isolated turtle heart recovered from mercurial poisoning by treatment with sodium thiosulfate. This case differs from the two cases described by Volini, Levitt and Martin [4] in that the electrocardiograms in their cases showed ventricular fibrillation and the patients died. We thus have electrocardiographic changes in patients exhibiting toxic reactions to the mercurial diuretics similar to those obtained experimentally in animals, indicating that the reaction is due to a direct action of the mercury ion on the heart muscle.

It is noteworthy that seven patients died six to 10 weeks after the reaction. One patient is in severe congestive failure at this writing, two months after the reaction. Apparently, the markedly diseased heart muscle is particularly sensitive to the mercurial diuretic. An immediate non-fatal reaction to a mercurial diuretic should then suggest a poor prognosis.

Summary and Conclusion

1. Reactions to mercurial diuretics in 18 patients are reported.

2. In 10 cases the reaction was delayed and was the result of dehydration. This type of reaction was associated with a high environmental temperature at the time of injection. Nine patients recovered with the administration of salt and water.

3. In eight cases the reaction occurred immediately after the injection. In seven cases reactions did not occur when the injections were given slowly and intermittently. In one case a reaction did not occur when the injections were preceded by sodium thiosulfate intravenously.

4. The occurrence of immediate reactions in a patient under dehydration therapy indicates a poor prognosis.

5. Reactions may be avoided by intermittent injections.

6. Because of excessive dehydration which may follow diuresis and the loss of chlorides through the sweat glands, the mercurials should not be given during a high environmental temperature.

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CASE REPORTS

EXFOLIATIVE DERMATITIS FOLLOWING PENICILLIN THERAPY *

By D. E. Nolan, Lt. Col., M.C., and George W. Pedigo, Jr., Capt., M.C., F.A.C.P., *Dayton, Ohio*

On reviewing the literature we have found no reports of exfoliative dermatitis due to penicillin therapy, hence this report.

Reactions to penicillin, however, are not infrequent and are generally not serious. Kolodny and Denhoff [1] in their study of 124 young men receiving penicillin therapy divided their reactions into the "immediate," those appearing within 24 hours, and the "delayed" which usually occur between seven and 14 days after the initiation of treatment. They report an incidence of 16 per cent "immediate" reactions, characterized by generalized rash, edema, gastrointestinal symptoms and "id" reactions. Seven per cent of all patients developed "delayed" reactions characterized by urticaria, swollen joints, edema, lymphadenopathy, generalized arthralgia, myalgia, and malaise. Flinn, McGee, Featherton, and Kern [2] in reviewing the literature found an incidence of 3 per cent of mild transient urticaria in patients receiving penicillin. Lyons [3] divided the reactions into those associated with penicillin from the same batch, which was thought to represent a reaction from an impurity, characterized by chills, eosinophilia, headache, flushing of the face, muscle cramps, nausea, and vomiting; and those reactions not related to any particular batch of penicillin, characterized by urticaria, fever, transient azotemia, and thrombophlebitis at the site of intravenous administration. Contact dermatitis following handling penicillin during its production and administration has been reported,[4, 5, 6] as has recurrent vesicular eruptions.[7] Various allergic manifestations [8, 9, 10, 11, 12, 13] have been reported due either to the drug or impurities in the commercial product. A typical urticarial reaction to penicillin consists of multiple wheals, angioneurotic edema, burning and itching of the skin. This usually lasts three to five days, and if the treatment with penicillin is continued the course of the urticaria is supposedly not affected. It has been stated [3] that if a patient has an urticarial reaction to penicillin on one occasion, he will probably not have this same reaction if penicillin is again used at a later date. Crisp, [14] however, reported a patient who developed urticaria while on penicillin therapy. The drug was then discontinued. Subsequently, on other occasions, penicillin was administered with the development of urticaria. The penicillin used was from different batches. Patch tests were positive. Crisp felt this represented a true allergy to penicillin.

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From the Medical Service, Veterans Administration Center, Dayton, Ohio.

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In addition to these reactions, Morris and Downing [15] report a patient who developed bullous dermatitis. Cormina et al.[10] reported two cases of erythematous vesicular eruption, one with erythema nodosum and one with a transient miliaria eruption, occurring during the treatment of 2000 soldiers on prolonged penicillin therapy. Meads et al.[16] describe the development of a morbilliform skin rash during penicillin treatment.

The following case report illustrates the occurrence of exfoliative dermatitis due to penicillin which to the best of our knowledge has not been previously reported.

Case Report

W. S., colored male, aged 60, was admitted to the hospital complaining of pain in the left anterior chest, of three weeks' duration. This pain was accentuated by deep breathing and movement. The pain was non-radiating and knife-like in character. He had an associated chronic cough which was productive of large quantities of yellow green material. He estimated that he expectorated about 400 c.c. of sputum each 24 hour period. The sputum was not foul smelling. He had lost about 30 pounds since the onset of the illness. He felt weak, tired easily, and had been having a low grade daily fever. The patient also stated he had vague abdominal distress which was not related to his meals and which was not aggravated by any particular type of food. He had never taken alkali for relief of this discomfort. On one occasion the patient passed a large tarry stool at which time he felt weak and faint. This occurred about five weeks before admission.

On physical examination the patient was a well developed and a well nourished colored male who did not appear to be acutely ill. There was limitation of expansion of the left chest. The percussion note at the left base was impaired over an area extending to the level of the fourth thoracic vertebra. The breath sounds were bronchovesicular over this area and numerous coarse moist râles were heard. The blood pressure was 108 mm. Hg systolic and 60 mm. diastolic. The pulse rate was 100. The physical examination was otherwise not contributory.

The laboratory study showed a negative urine. The red blood cell count was 3,480,000 with 71 per cent hemoglobin. The white blood cell count was 15,800 with 78 per cent polymorphonuclear cells. The electrocardiogram was negative. Sputum studies for acid-fast bacilli were negative. Roentgen-ray of the heart and lungs showed an area of heavy infiltration in the midportion of the left lung in an area surrounding the left hilum. There was a large cavity in the center of the opacity, confirming the clinical diagnosis of lung abscess.

A gastrointestinal roentgen-ray series showed evidence of a duodenal ulcer. Cultures of the sputum showed the predominant organisms to be a gram negative diplococcus and a gram negative bacillus.

The patient was placed on postural drainage, sulfadiazine, iron, and a high carbohydrate and high vitamin diet. He improved rapidly. The temperature became normal. His clinical course showed improvement as demonstrated by improved appetite and sense of well being. His sputum decreased and his roentgenogram showed definite improvement with diminution in the size of the abscess cavity. After two weeks sulfadiazine therapy was discontinued and a course of penicillin was started, 15,000 units of penicillin being given every three hours. After the fifth dose of penicillin the patient began to complain of generalized itching of the skin, and a few wheals appeared. The skin became very red over a generalized area. The penicillin was discontinued, and the urticaria and associated skin lesions cleared within 24 hours. Fourteen days later the patient was again placed on a course of penicillin with a dosage of 20,000 units every three hours. After the fourth dose the patient de-

veloped a diffuse erythematous appearance of the skin, he became nauseated and perspired freely. The skin manifestations, although generalized, were more noticeable on the legs, face, neck, and arms. To a lesser degree it was also present over the trunk. This erythematous appearance persisted, although the penicillin was discontinued. No evidence of wheals or urticaria was noted. In about three days, the skin over the involved area began to exfoliate with thin flakes and thickened scales appearing. The scales were a dirty gray color and the underlying skin was red and shiny. This condition persisted, and although it did not become as extensive or as severe as many cases of exfoliating dermatitis, there was still evidence of exfoliation four weeks later. A patch test with this penicillin was strongly positive. Control tests with normal saline were negative. Three weeks later, using a different batch and brand of penicillin, patch and intradermal tests were negative.

Comment

No history of a previous fungus infection or treatment with penicillin could be elicited. Before assuming the skin reaction to be the result of some impurity in the penicillin, the findings of Welch and Rostenberg [17] should be considered. They report the occurrence of hypersensitivity of the tuberculin type to crystalline penicillin sodium. In addition, Chow and McKee [18] have reported that the combination of crystalline penicillin and human albumin produces a penicillin-protein complex. It is entirely possible that some of these reactions to penicillin are due to sensitivity to the pure drug itself rather than impurities. However, inasmuch as the first patch test was strongly positive and later patch and intradermal tests, using a different batch and brand of penicillin, were negative, it would appear that the exfoliative dermatitis in this patient was due to some impurity in the original batch of penicillin.

Summary

A case of exfoliative dermatitis following penicillin therapy is presented.

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ACUTE SYPHILITIC NEPHROSIS: REPORT OF A CASE*

By Albert Heyman, M.D., and Charles E. Brown, M.D., *Atlanta, Georgia*

For many years syphilis has been thought to produce kidney damage, and various renal manifestations have been attributed to this disease. In most of the cases that have been reported, there has been no proof that the *Treponema pallidum* was the direct cause of the kidney damage. Nevertheless, there are several renal syndromes which have been found to be so definitely associated with syphilis that their syphilitic origin is not generally questioned. Of these, the most distinct clinical entity is the acute nephrotic state associated with secondary syphilis. In this syndrome the changes of typical nephrosis occur, but the condition usually clears rapidly, leaving no evidence of persistent renal impairment. Such cases are uncommon, and a review of the literature by Herrmann and Marr [1] reveals that up to 1935 there had been only nine cases reported in which the necessary studies to document the diagnosis had been made. Recently, five additional cases have been described.[2, 3, 4] Because of the relative rarity of this condition, the following case of acute nephrosis associated with secondary syphilis is reported.

Case Report

D. H., a 31 year old Negress, was admitted to Grady Memorial Hospital because of oliguria, edema and a generalized skin eruption.

Twelve days prior to admission, the patient first noted edema of the face and lower extremities and the onset of a progressive oliguria. Three days later a generalized non-pruritic rash appeared and the lymph nodes in the neck and behind the ears became enlarged. By the time of admission the oliguria had progressed to the extent that the patient was voiding once a day.

For 12 years preceding this illness, the patient had been seen on numerous occasions in the out-patient clinic for minor surgery and prenatal care. During this period there were no symptoms suggesting heart or kidney disease. Her record showed

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From the Clinic for Genitoinfectious Diseases, the Medical Service of Grady Memorial Hospital and the Department of Medicine of Emory University School of Medicine, Atlanta, Georgia.

repeated urine specimens to be normal, a normal electrocardiogram, and absence of any findings of cardiac or renal damage. Blood pressure determinations varied, with one exception, from 127 to 140 mm. mercury systolic and 90 to 95 mm. mercury diastolic. (A single reading of 160 mm. mercury systolic and 80 mm. mercury diastolic was recorded in the eighth month of pregnancy, but this elevation was not sustained.)

The past history was negative for symptoms or treatment of syphilis. The serologic tests for syphilis had been negative repeatedly and a negative Kahn test had been obtained 18 months before admission.

On admission, the patient's temperature was 99° F. The pulse and respiratory rates were normal and the blood pressure was 128 mm. mercury systolic and 80 mm. diastolic. The face and eyelids showed swelling, and a moderate degree of pitting edema was present in the lower extremities. A dry follicular eruption covered the face, trunk and extremities, but did not include the palms or soles. No mucous membrane lesions were noted in the mouth or nose. The pupils reacted well to light and on accommodation. Ophthalmoscopic examination revealed normal fundi with no changes of the optic discs or retinal vessels. There were firm, discrete, enlarged lymph nodes palpable in the pre-auricular, mastoid, occipital and posterior cervical regions. The lungs were normal to auscultation and percussion; the heart, normal with no murmurs or evidence of enlargement. The spleen and liver could not be palpated. The external genitalia were normal. On speculum examination there appeared a small ulceration of the vaginal mucosa near the cervix. The cervix itself was normal, and examination of the adnexae revealed no masses or tenderness. The deep reflexes were physiologic.

Laboratory Data. The urine on admission contained albumin 4 +, with rare red and white blood cells, and many hyaline casts per high power field. Repeated urine examinations during the first few days in the hospital showed a maximum specific gravity of 1.020, albumin 4 +, and a few casts. The 24-hour urine specimen contained 4.58 gm. of protein. There was 50 per cent phenolsulfonphthalein excretion in one hour. The hemoglobin was 9 gm. per 100 c.c., and the red blood cell count was 3,900,000 per cu. mm. The white blood cell count was 17,700 per cu. mm. with a slight increase in neutrophiles. The sedimentation rate by the Westergren method was 114 mm. in one hour. Blood chemical determinations showed the non-protein nitrogen to be 24 mg. per 100 c.c., cholesterol 109 mg. per 100 c.c., total protein 7.6 gm. per 100 c.c. with 2.6 gm. of albumin and 5 gm. of globulin.

The electrocardiogram was normal and the basal metabolism rate was + 14. Teleoroentgenogram of the chest showed slight tortuosity of the aorta, but no cardiac enlargement. Two dark field examinations of serum from the vaginal ulcer revealed no *Treponema pallidum*, but biopsy of the skin showed secondary syphilis. Repeated blood Kahn tests were positive with a titer as high as 800 units.

Treatment and Course. The patient's temperature remained below 99° F. during her hospitalization. Fluids were not restricted, and a high protein diet was given at first, but later this was changed to a low salt diet. Anti-syphilitic therapy was withheld for the first eight days, during which time the patient lost eight pounds in weight. The urine output varied between 1090 c.c. and 1810 c.c. per day. The edema diminished noticeably and the albuminuria decreased from 4 + to 1 + by the nitric acid ring test. The daily total urine protein fell from 4.58 gm. on admission to 0.374 gm. by the eighth day. Casts disappeared from the urinary sediment. The serum cholesterol increased from 109 mg. to 150 mg. per 100 c.c. The follicular eruption showed little, if any, change.

On the ninth hospital day, mapharsen therapy was begun. Doses of 30 mg. were given intravenously three times in the first week and 45 mg. every second day thereafter. There was no Jarisch-Herxheimer reaction. The rash began to subside after three or four days and had almost disappeared by the eleventh hospital day. The

albuminuria continued to decrease, and tests for albumin were all negative after the fourteenth hospital day. The total serum protein remained approximately 7.8 gm. per 100 c.c., but the albumin fraction increased from 2.6 gm. to 3.8 gm. per 100 c.c.

When transferred to the out-patient department on the thirtieth hospital day, the patient had a normal urine, no edema, and a Kahn reaction of 120 units. Three months later, after a total of 36 injections of mapharsen and six injections of bismuth, the Kahn reaction was doubtful. At that time the blood pressure was 130 mm. mercury systolic and 100 mm. diastolic. The urine was normal, with 35 per cent phenolsulfonphthalein in 15 minutes; the non-protein nitrogen was 25 mg. per 100 c.c.; the serum cholesterol, 200 mg. per 100 c.c.; and the total serum protein was 8 gm., with 4 gm. of albumin.

Discussion

This patient, with no evidence of previous renal damage, abruptly developed oliguria, edema, albuminuria, cylindruria and depletion of the serum albumin. Concurrently, manifestations of secondary syphilis appeared with a Kahn reaction of high titer. The blood pressure was not elevated, and there were no eyeground changes suggesting previous vascular disease. The phenolsulfonphthalein excretion and serum non-protein nitrogen were both normal. The findings in this case satisfy the criteria set forth by Herrmann and Marr [1] for the diagnosis of acute syphilitic nephrosis.

In the cases of acute syphilitic nephrosis that have been reported, the illness has been relatively benign. The early complaints are mild and consist of malaise, headache and myalgia, common systemic symptoms in secondary syphilis. The onset of edema is abrupt and frequently accompanied by oliguria. On physical examination the striking findings are edema of the face and extremities, skin and mucosal lesions of secondary syphilis, and generalized lymph node enlargement. Evidences of chronic renal disease are invariably absent and the blood pressure and retinal vessels are normal. Albuminuria is a constant finding and the amount of protein excreted is sometimes extremely high. Moore [5] reported a case in which 20 gm. of protein were excreted per day, and Karnoven [6] noted an excretion of 110 gm. of protein in a day. However, 10 gm. to 20 gm. of protein per liter of urine are more commonly found. Hyaline and granular casts are present in most cases and a few white and red blood cells are usually seen. Excretion of phenolsulfonphthalein is normal and the ability of the kidneys to concentrate is not impaired. The blood non-protein nitrogen level is also normal.

The total serum proteins are lowered by depletion of the albumin fraction with resulting alteration of the albumin-globulin ratio. The increased serum globulin noted in our case is not the usual finding in nephrosis. This patient showed a negative skin and complement fixation reaction for lymphogranuloma venereum, and the cause of the hyperglobulinemia was not determined.

Serum cholesterol values are usually high, but levels as low as 150 mg. per 100 c.c. or less have been recorded. The basal metabolic rate is usually low and may show a rise coincident with antisyphilitic therapy. Attempts to find *Treponema pallidum* in the urine have been unsuccessful in these cases, although they have been reported in syphilitic patients not showing manifestations of renal disease.[2]

The syndrome of acute syphilitic nephrosis usually responds promptly to antisyphilitic therapy, but occasionally the condition undergoes a spontaneous

remission. In three of the 14 reported cases the nephrotic state developed after arsenical therapy had been instituted, and the question arose as to a possible nephrotoxic action of the arsenical. However, with continuation of treatment with arsenicals all evidence of nephrosis disappeared. Inasmuch as usual doses of the arsenicals have been known to cause little if any kidney injury, it is conceivable that these cases represent a Herxheimer reaction with exacerbation in Treponema-infected kidneys.

Various other syphilitic renal conditions have been described in the literature. These syndromes vary from a mild, transient albuminuria to severe hemorrhagic nephritis or chronic nephrosis [1] requiring months or years of antisyphilitic treatment. Most of these cases have little evidence to substantiate a syphilitic etiology, for often no thorough study was made to exclude other causes of the nephropathy. The clinical diagnosis of syphilitic renal disease is difficult and can probably never be established with absolute certainty, for there is no indisputable clinical evidence to support the rôle of syphilis in the production of a specific renal syndrome. Neither the finding of *Treponema pallidum* in the urine nor the apparent beneficial effect of antisyphilitic treatment is sufficient evidence for the diagnosis of syphilitic renal disease. The interstitial nephritis described by Rich [7] is probably of syphilitic origin, but this condition can only be diagnosed histologically for there are no associated clinical characteristics.

The acute nephrosis associated with secondary or early syphilis is thus the only renal syndrome resulting from acquired syphilis which can be recognized clinically. The occurrence of a similar acute benign nephrosis in non-syphilitic adults is distinctly rare, if it ever occurs at all.

Summary

A case of acute benign nephrosis associated with secondary syphilis is reported, and the difficulties encountered in the clinical diagnosis of syphilitic renal disease are discussed.

Addendum. After this paper was submitted for publication, two cases of acute syphilitic nephrosis treated with penicillin have been reported: Tucker, H. A.: Penicillin treatment of acute syphilitic nephrosis and iritis, report of a case: Am. Jr. Med. Sci., 1946, cxi, 718; and Barr, J. H., Jr., Cole, H. N., Driver, J. R., Leas, R. D., Miller, Max, and Strauss, L. S.: Acute syphilitic nephrosis successfully treated with penicillin, Jr. Am. Med. Assoc., 1946, cxxxi, 741.

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A CASE OF AGRANULOCYTOSIS OCCURRING DURING THE COURSE OF PENICILLIN THERAPY *

By DAVID M. SPAIN, M.D., and THOMAS B. CLARK, M. D., *New York, N. Y.*

As yet, there have been no reports of the occurrence of agranulocytosis resulting from the use of penicillin. As a matter of fact, penicillin is one of the most frequently used therapeutic agents in agranulocytosis in order to prevent or to combat the associated infection. The following case, although not conclusive, suggested that on rare occasions penicillin may produce agranulocytosis.

CASE REPORT

The patient, a 54 year old white male, was admitted on October 12, 1945, to the First Surgical Division of Bellevue Hospital with the complaint of abdominal pain of five days' duration. He presented the classical symptoms and signs of acute intestinal obstruction. His previous history was non-contributory. On admission his temperature was 101.8° F., pulse 110, respirations 18, and blood pressure 120 mm. Hg systolic and 90 mm. diastolic. At this time, the white blood cell count was 13,150 with a normal differential count.

After proper preparation and with the start of penicillin (see chart for list of medication and blood counts), he was sent to the operating room and a cecostomy was performed. At this time the site of obstruction was not determined. The following day a generalized erythematous macular skin rash appeared. The dermatologist, upon consultation, stated that this rash was consistent with those appearing as a result of penicillin sensitivity. On the third day post-operatively, the temperature rose to 104.0° F. and he became psychotic. At this time the abdomen was soft and there was no distention present. A mild infection was present at the cecostomy site. The remainder of the physical examination was negative. Later in the day the white blood cell count was 2,800 with a marked reduction of the number of polymorphonuclear leukocytes (15 per cent). The following day (fourth day postoperatively), the temperature remained about 104.0° F., and another white blood cell count was 100 with no polymorphonuclear leukocytes to be seen. This count was repeated and checked by several observers with essentially the same results.

At this time, the pharynx was injected and pustules were present on the palate. Penicillin was then discontinued, a transfusion of 1000 c.c. whole blood was given, and sulfadiazine medication was started. The rash was now quite pronounced. Sixteen hours after discontinuing penicillin, the white blood cell count was 6,000 with polymorphonuclear leukocytes present in almost normal proportions. The red blood cell count was 6,500,000. That evening, the temperature dropped to 102.0° F. and the white blood cell count was then 5,200. The temperature went down to 101.0° F. on the next day and another white blood cell count was 5,000. His abdomen was soft, but a mild wound infection was still present.

On October 19, 1945, the leukocyte count was 10,700, but he became restless, vomited frequently, the blood pressure dropped and he died.

Postmortem examination revealed that there was a constricting annular carcinoma of the sigmoid colon. The cecostomy was widely patent. There was no evidence of peritonitis, but a mild necrosis and infection were present at the cecostomy site. The bone marrow revealed no abnormalities. Considerable pulmonary edema was present.

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From the Laboratories of Pathology, Bellevue Hospital, and First Surgical Division (Columbia University).

Chart Listing Medication and White Blood Counts

Date	Time	Dosage of Penicillin	Other Medication	W.B.C.
10/12/45	9:45 p.m.	50,000 Units	Morphine sulfate, 0/01 gm. Scopolamine, 0/005 gm. Vitamin K (2 ampules)	13,150
10/12/45	11:45 p.m. (Post-op.)	50,000 Units	Prostigmine, 1/2000, 1 ampule, Q4H × 12 Morphine sulfate, 0/01 gm., Q4H, PRN.	—
10/13/45	—	20,000 Units Q3H (This was given for 23 doses)	Vitamin C, thiamine, 5% glucose-saline infusion	Skin rash appeared
10/14/45	—	—	Demerol, 100 mg. Phenobarbital, 0/45 gm.	—
10/15/45	—	—	—	2,800—15% PMN'S.
10/16/45	—	Discontinued	—	100–0 PMN'S.
10/16/45	(1,000 c.c. of whole blood)			
10/17/45	16 hrs. after discontinuation of penicillin	—	Sulfadiazine, sodium bicarbonate Morphine sulfate, 0/01 gm. Sodium phenobarbital, 0/6 gm.	6,000—45% PMN'S. 5,200
10/18/45	—	—	—	5,000
10/19/45	—	—	Morphine sulfate, 0/01 gm. Digalin (2 ampules)	10,700

The anatomic diagnosis was adenocarcinoma of the sigmoid colon, recent cecostomy, mild wound infection and pulmonary edema.

In this case, in addition to the penicillin, there was other medication. This is listed on the chart. However, it does not seem likely that the other medication had any causal relation to the onset of the agranulocytosis. Some of the same medication was continued during the agranulocytosis and was given afterwards without any effect on the white blood cell count. The appearance of the skin rash, said to be typical of that seen in penicillin sensitivity, along with the rise in the white cell blood count soon after the cessation of penicillin, appears to be significant. There does not seem to have been sufficient infection present to act as a causal agent for the agranulocytosis. Although the evidence is not conclusive, it is believed this report is justified.

Summary

A case is presented in which penicillin may have been responsible for the development of agranulocytosis.

HYPERTENSION AND THE KIDNEY *

By CARL A. WATTENBERG, M.D., *St. Louis, Missouri*

UNILATERAL non-nephritic kidney disease can be the cause of hypertension, and this hypertension often can be relieved by nephrectomy. This fact has been shown definitely. Many case reports have been published since the work by Goldblatt [1] and his associates, which should remove any doubt that hypertension may result from certain types of pathological unilateral renal changes. It is true that some of these cases were reported too soon following the nephrectomy, but the urologist still sees nephrectomy as a definite cure for hypertension in certain cases.

Certainly there always should be a careful urological examination of all cases of hypertension before one considers a denervation operation or medical treatment such as potassium thiocyanate. The so-called essential hypertension should have this urological study early in the disease before there can occur an arteriolar disease of the other kidney. If this change does occur then the possible cure is lost.

Flocks [2] recently discussed the method of study for a case of hypertension. Some of the necessary steps included a flat film to give the renal outline, a retrograde pyelogram to obtain the renal pelvis, which together gave an estimate of the renal mass. The phenolsulphonphthalein output from each kidney was determined separately following the intravenous injection. This was to give an estimate of the tubular function and, indirectly, of the blood flow through the kidney. During this same seriod the urea output was estimated and the urine studied for chemical or cellular abnormalities.

Braasch,[3] Barker [4] and Walters [3, 4] have shown in their recent studies that the highest incidence of hypertension occurred in patients who had a unilateral atrophic pyelonephritis. However, all cases with unilateral atrophic pyelonephritis do not have hypertension, and all cases which do have hypertension are not cured by nephrectomy of the unilateral diseased kidney.

Goldblatt [1] showed that impairment of renal circulation even when unilateral can be a cause of hypertension. Since Goldblatt's demonstration of a renal origin for hypertension, clinicians have tried to show a causal relationship between various organic lesions of the kidney and abnormal elevations of the blood pressure.

Despite the vast experimental and clinical studies on the etiologic relationship between renal change and hypertension, one cannot be sure whether or not the hypertension is of renal origin. When there is doubt, the patient should have the benefit of a nephrectomy of the unilateral diseased kidney, provided the other kidney has good function.

Cases of hypertension observed at the Mayo Clinic and reported by Braasch [5] showed that the percentage of patients having clinical or roentgenographic evidence of unilateral "surgical" or non-nephritic renal disease was about 2.5 per cent of all the hypertensive cases studied. It was shown also in his study that less than 0.5 per cent of all hypertensive cases were suitable for nephrectomy as

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From the Department of Surgery, Urological Division, Washington University School of Medicine, Barnes Hospital, St. Louis, Mo.

a cure for hypertension. In our study of the cases at Barnes Hospital the percentage has been less than 0.5, the best results being obtained in the younger individuals.

The following case is presented since this patient had such marked benefit following her nephrectomy for unilateral kidney disease.

Case Report

Mrs. R. P. A., a white American housewife, 27 years of age, was admitted to Barnes Hospital for the second time March 30, 1943. She was complaining of severe frontal headaches, dizzy spells and nausea of three years' duration. She had had occasional ankle edema and pain in the right kidney region for several years, often nocturia, with mild burning on urination.

In 1941, on December 5, while in Barnes Hospital, she had complained of prolonged headaches, frequent colds and nasal obstruction. A submucous resection and spheno-ethmoidectomy were done for these complaints but with no benefit. Blood pressure during this visit was 150 mm. Hg systolic and 100 mm. diastolic. The urine contained one plus albumin. Catheterized urine culture had a growth of many *E. coli* organisms.

This patient, on her second admission to the hospital, was under the care of Dr. Edward Massie, an internist at Barnes Hospital, and was referred by him to me for a urological study.

The patient stated that she was well and healthy until her first pregnancy eight years before. During the last trimester she developed albuminuria and edema. Following the delivery she again was in good health. The second pregnancy six years before resulted in a spontaneous termination. Three years previously she had her third pregnancy and was getting along satisfactorily, but had a spontaneous abortion during the fifth month. Again she was feeling fine until the last trimester of her fourth pregnancy which terminated in an induced normal delivery at the eighth month, 11 months before the second admission to Barnes Hospital. During the last trimester of this fourth pregnancy, she developed a marked elevation of blood pressure with generalized edema. Following this delivery the generalized edema disappeared, but she continued to have occasional periods of edema of the ankles, hands and face. The severe left frontal headaches progressed and were accompanied by nausea and vomiting on occasion.

During the past several years the patient also had had pain in the region of the right kidney. This never was severe or colicky. It was described as a discomfort and an ache. She had periods of frequency and mild burning on urination with nocturia during the past year. There was no family history of renal or cardiac disease or migraine. The past history was essentially negative except for an appendectomy when 12 years of age, and for findings given above.

The general physical examination was negative except for the blood pressure which was 210 mm. Hg systolic and 140 mm. diastolic. The patient was well-developed and well-nourished. The eyegrounds showed each disc well outlined with no exudates or hemorrhages. The heart rate was regular with no murmurs. There was a slight enlargement of the heart to the left but no evidence of decompensation. The lungs were clear. On palpation and examination of the abdomen neither kidney could be palpated, but slight resistance and tenderness were noted in the region of the right kidney.

The blood Wassermann reaction was negative, hemoglobin 14 gm., the red cell count 4,300,000, the white cell count 7,400, and the differential count and platelets were normal. The non-protein nitrogen was 20 mg. per cent. The maximum urea clearance was 78 per cent and the standard urea clearance was 50 per cent. Fasting blood

sugar was 77 mg. per cent. Urinalysis of a catheterized urine specimen showed albumin one plus, and a centrifuged specimen stained with methylene blue revealed many rods and scattered pus cells. Basal metabolic rate was minus 1 and plus 5 per cent. The electrocardiogram was indeterminate and showed no myocardial damage.

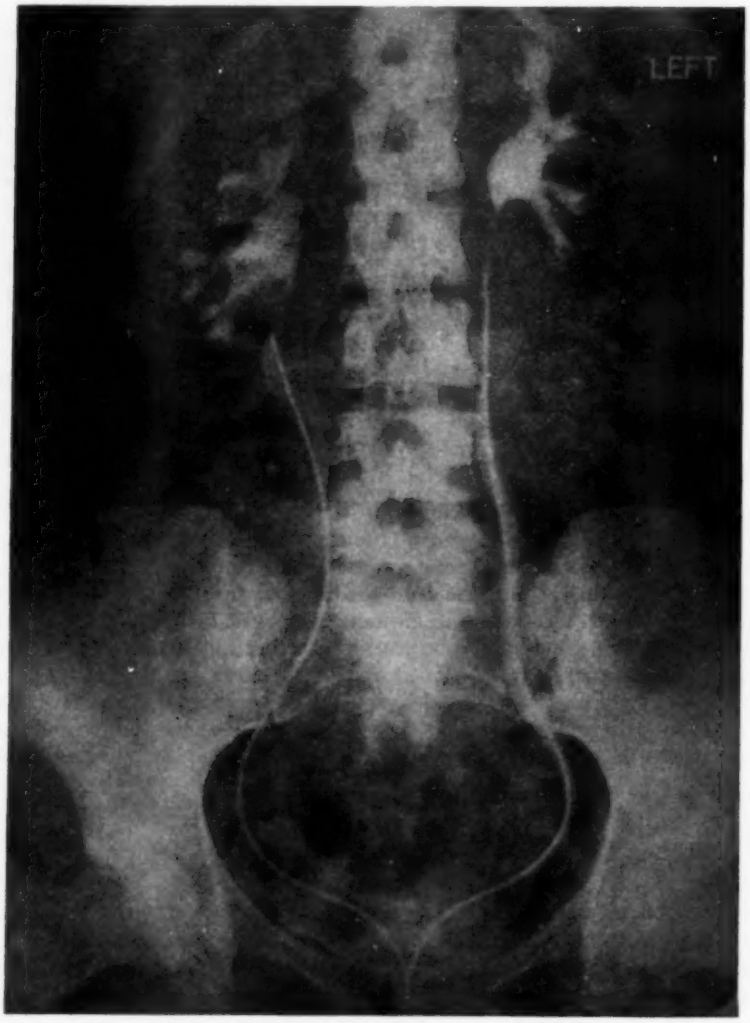

FIG. 1. Retrograde pyelogram showing blunting and irregularity of the right calyces. The left kidney pyelogram is normal.

Cystoscopic examination revealed a generalized mild cystitis. Urine from the right kidney contained many rods as shown by culture and films stained with methylene blue. The urine from the left kidney was negative. One c.c. of phenolsulphonphthalein was given intravenously and appeared from the right kidney catheter in five minutes, and from the left kidney catheter in three minutes. The 10-minute function from the right kidney was 8 per cent and 12 per cent from the left. The plain film was normal

except that the right kidney shadow was slightly smaller than the left kidney shadow. The left pyelogram was normal, whereas the right pyelogram showed a blunting and irregularity of the calyces with some irregularity of the pelvis, as shown in figure 1.

A diagnosis of right atrophic pyelonephritis was made. The patient was discharged from the hospital for rest on April 3, 1943. She was given mandelic acid.

The patient was seen again and readmitted to Barnes Hospital June 7, 1943. The burning and frequency were much improved, but blood pressure was 220 mm. Hg systolic and 140 mm. diastolic and the headaches were severe.

A right nephrectomy was done June 9, 1943. There was a marked fibrosis surrounding the kidney and its pedicle. The outer surface of the kidney was lobulated, as seen in figure 2. The kidney was small, weighing 70 gm. The cut surface of the cortex appeared atrophic and measured about one-half centimeter in its greatest thickness (figure 3).

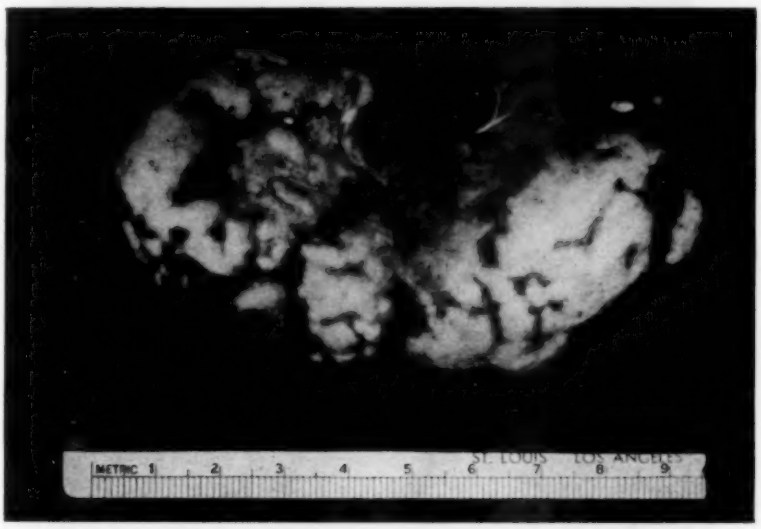

FIG. 2. Photograph of right kidney showing the outer surface scarred and lobulated. The kidney weighed 70 grams.

Microscopically, the cortex of the kidney showed interstitial fibrosis, inflammatory changes and round cell infiltration. There was an intertubular edema and fibrosis. The capillary tufts were adherent to Bowman's capsule and in several areas there was complete hyalinization, as shown in figures 4 and 5. In a few areas thick collections of inflammatory cells were present and suggested abscess formation. The small and medium-sized arteries showed intimal proliferation and some fibrosis of the media (figure 6). Section of the renal artery showed its lumen to be patent. The wall, however, was somewhat thickened.

Following the operation, there were no more attacks of dizziness nor headaches. The blood pressure gradually became lower, as seen in table 1. The patient was discharged from the hospital on her fourteenth post-operative day, with a blood pressure of 140 mm. Hg systolic and 100 mm. diastolic. She was feeling fine and stated "I feel as though I have a new lease on life." She was comfortable and had no headaches, nausea, vomiting or dizzy spells. Since her discharge from the hospital she has been seen on a few occasions and always without a complaint.

On January 10, 1944 her blood pressure was 158 mm. Hg systolic and 96 mm. diastolic. On May 8, 1944, it was 148 mm. Hg systolic and 98 mm. diastolic. Heart sounds were of normal quality and pulse was normal. Urine showed no infection when stained and contained no albumin. She has been working every day and has gained 20 pounds. On August 8, 1944 her blood pressure was 126 mm. Hg systolic and 86 mm. diastolic and she had no complaints.

On January 12, 1945 the patient's blood pressure was 120 mm. Hg systolic and 80 mm. diastolic and after activity it was 140 mm. Hg systolic and 100 mm. diastolic. The urine was negative.

FIG. 3. Photograph of inner surface of right kidney. The cortex is atrophic and measures about one-half centimeter in thickness.

A two year post-operative examination was made June 10, 1945. The patient's blood pressure was 150 mm. Hg systolic and 104 mm. diastolic after activity, and at rest it was 128 mm. Hg systolic and 88 mm. diastolic in the left arm and 132 mm. Hg systolic and 92 mm. diastolic in the right arm. The heart sounds were normal, and there was no cardiac enlargement. Her weight was 139 pounds, and she had no headaches or complaints.

A catheterized urine specimen was clear and contained no albumin or casts. A centrifuged specimen, stained with methylene blue, contained no organisms. Her blood non-protein-nitrogen was 13 mg. per cent. One c.c. of phenolsulphonphthalein given intravenously produced a 35 per cent output in 20 minutes.

The patient is considered cured of hypertension caused by unilateral renal disease.

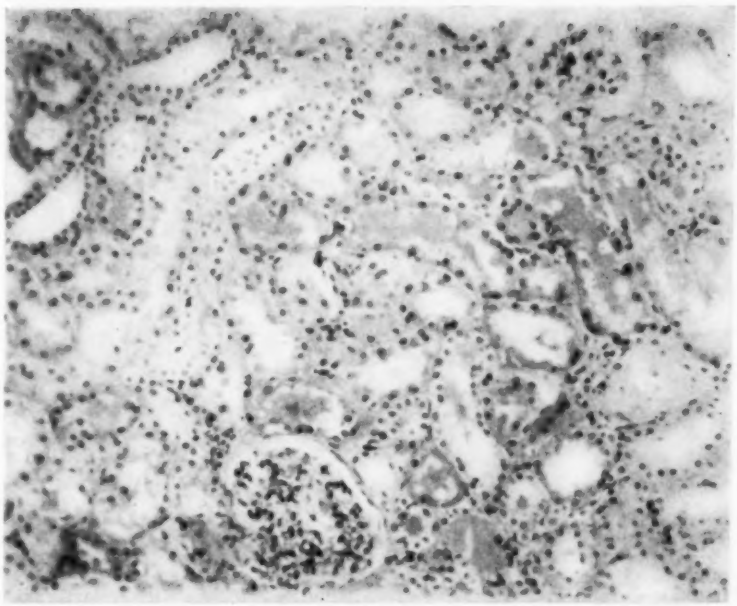

FIG. 4. Photograph of microscopic section from right kidney showing intertubular edema and fibrosis.

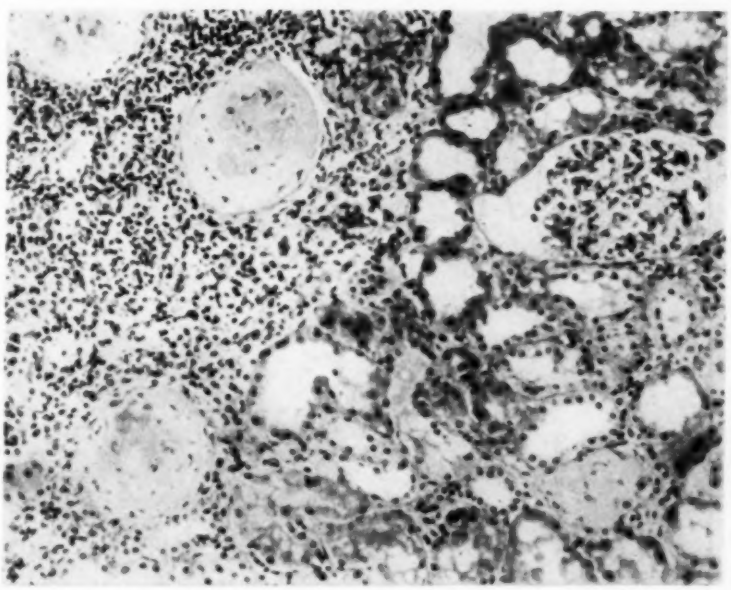

FIG. 5. Microscopic section of right kidney cortex showing interstitial fibrosis, inflammatory changes with round cell infiltration. Some of the glomeruli show complete hyalinization.

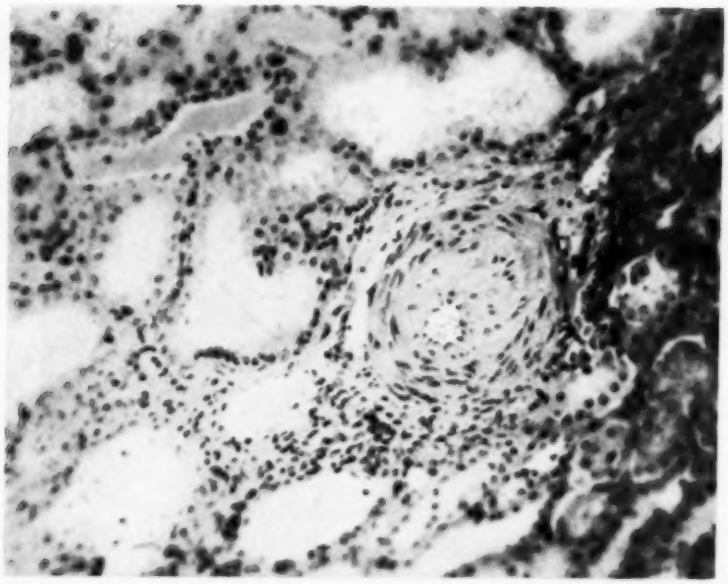

FIG. 6. Photomicrograph from right kidney showing an arteriole with endarteritis obliterans.

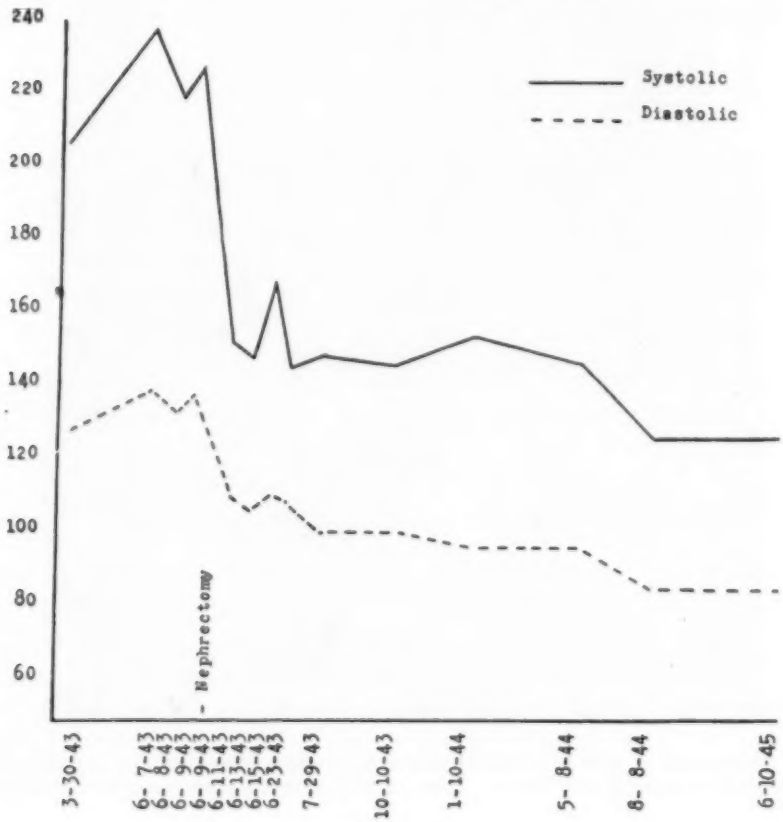

TABLE I

Conclusions

1. Unilateral renal disease, such as chronic atrophic pyelonephritis, can cause hypertension and may be cured by nephrectomy.

2. Urological examination should be carried out early in the course of hypertension if possible, before arteriolar disease of the other kidney can occur.

3. Careful urological examination should be made on all cases of hypertension before a denervation operation is performed, or before potassium thiocyanate therapy is instituted.

4. Report is made of a case which had a blood pressure of 220 mm. Hg systolic and 140 mm. diastolic, March to June 1943. Nephrectomy was done June 9, 1943. Blood pressure August 8, 1944, was 126 mm. Hg. systolic and 86 mm. diastolic. Two years post-operatively, June 10, 1945, the blood pressure was 128 mm. Hg systolic and 88 mm. diastolic. The patient had complete relief from symptoms.

Note: On Sept. 10, 1946, patient's blood pressure was 126 mm. Hg systolic and 88 mm. diastolic. Urine was negative for albumin and infection.

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EDITORIAL

RADIOACTIVE PHOSPHORUS AS A THERAPEUTIC AGENT

RADIOACTIVE phosphorus has now been used therapeutically for several years, chiefly in the treatment of leukemia and polycythemia. Although the number of cases treated and the period of observation are still small, enough has been learned to warrant some tentative conclusions as to the value and limitations of this drug.

When ordinary phosphorus (P^{31}) is bombarded with deuterons (nuclei of heavy hydrogen) emitted at high speed by a cyclotron, an additional neutron is forced into the nucleus of some of the phosphorus atoms. This increases the mass of the atom (P^{32}), which now contains 15 protons and 17 neutrons. The number of electrons in the atom, which is identical with the number of protons present, is not changed, however, and therefore the new radioactive atom (P^{32}) is identical in its chemical reactions with the original atom (P^{31}) and can replace the latter in any inorganic or organic compounds into which phosphorus enters.

P^{32} is unstable, and one of the neutrons tends to change into a proton with simultaneous emission of an electron (beta ray), which exerts radioactivity on tissue cells or other material which it may reach. The mass of the new atom is not changed, but as it contains 16 neutrons and 16 protons and therefore 16 electrons, it is quite different chemically—it has become sulfur. The rate of this change is constant and is such that half of the radioactive phosphorus is converted into sulfur in 14.3 days (the "half-life" of P^{32}).

The radioactivity of a preparation can be measured with fair precision by means of a suitable electroscope or a Geiger counter. The unit is the millicurie, the amount of radioactivity produced by the disintegration of 37,000,000 atoms per second. No alpha or gamma rays, only beta rays are produced.

The amount of phosphorus converted into the radioactive form by the cyclotron varies with the exact conditions of the experiment but is relatively minute—ordinarily in the range of one part in one or two millions.

Phosphorus so treated can be used in making dibasic sodium phosphate or other preparations which can be administered to patients orally or intravenously. Isotonic solutions from freshly prepared material ordinarily contain about 0.2 to 0.4 millicuries per c.c.

The absorption, excretion and distribution of P^{32} in the tissues have been extensively studied by measurement of their radioactivity. Apparently the body tissues utilize P^{31} and P^{32} indifferently, the relative amount of each taken up depending solely upon the proportion of each type in the plasma and tissue fluids. Other factors being constant, therefore, the higher the concentration of P^{32} in the solution administered and the smaller the quan-

tity of P^{31} ingested in the food and from other sources, the greater will be the absolute amount of P^{32} taken up by any given tissue.

Following oral administration, about 75 per cent of the P^{32} is absorbed. Following intravenous administration, in normal individuals from 25 to 50 per cent is excreted in the urine and feces during the first four to six days. After this, the rate of excretion falls to about 1 per cent per day. In leukemia a larger proportion of the P^{32} is retained.

The relative amount of P^{32} taken up by the various tissues after the administration of a single dose varies greatly, depending upon the amount of phosphorus in the tissue and particularly upon its metabolic activity and the rate of cell multiplication. At first high concentrations are found in the bone marrow, liver, spleen and lymph nodes and somewhat lower in kidney and muscle. Later high concentrations are found in bone. Neoplastic and leukemic tissue takes up much more P^{32} than normal tissue.

The effect exerted on the tissues by P^{32} depends entirely upon the beta ray emitted when the atom disintegrates, and in general is similar to that of roentgen radiation. Although the beta ray is emitted with enough energy to penetrate about 7 mm. of tissue or fluid, its effect is largely exerted in situ and is relatively concentrated on those cells which absorb it in largest amount. Radiation applied externally must reach normal and pathological cells in equal concentration, and any specific effect it may exert on the latter must depend simply upon a greater inherent susceptibility of the pathological cells to its action. Furthermore the length of life of P^{32} is sufficient to maintain a substantial activity continuously for some days, whereas roentgen radiation can be applied only for brief intermittent periods. It would be possible, therefore, that these differences in the application of the energy might give P^{32} an advantage over roentgen radiation as a therapeutic agent.

Lawrence et al.[1] in 1939 were the first to report the treatment of chronic myelogenous leukemia (two cases) with radioactive phosphorus. Since then several reports have appeared, of which only two will be discussed. Erf, Tuttle and Lawrence[2] in 1941 reported a series of 46 cases of myelogenous leukemia treated with P^{32}. The eight cases of acute leukemia were not benefited. Of the 38 cases of chronic leukemia, partial remissions were obtained in 11 and complete remissions in five, whereas 21 had died. Many of these patients had previously received other types of treatment, were in advanced stages of the disease and were unfavorable subjects for any therapeutic experiment. Those who had had roentgen radiation previously responded poorly as a rule. Those who did respond favorably showed a progressive fall in the leukocyte count to normal or approximately normal values, with a reduction or even a virtual disappearance of primitive leukocytes from the peripheral blood. With this there was a rise in the erythro-

[1] Lawrence, J. H., Scott, K. G., and Tuttle, L. W.: Studies on leukemia with the aid of radioactive phosphorus, Internat. Clin., 1939, iii, 33.

[2] Erf, L. A., Tuttle, L. W., and Lawrence, J. H.: Clinical studies with the aid of radiophosphorus. IV. The retention in blood, the excretion and the therapeutic effect of radiophosphorus on patients with leukemia, Ann. Int. Med., 1941, xv, 487.

cyte count and hemoglobin, usually to normal values. There was a corresponding improvement in subjective symptoms. The spleen and liver usually diminished in size, and in a few cases they could no longer be felt. Two patients had maintained "essentially complete remissions" for nearly two years.

Reinhard et al.[3] have recently reviewed the subject and reported their own results in 39 cases of myelogenous leukemia treated with P^{32}. No benefit was obtained in any of the nine acute cases. Of the 30 cases of chronic myelogenous leukemia, 12 had died and 18 were living at the time of the report. Many were unfavorable cases in an advanced stage of the disease. Eleven cases had been followed for a year or more, and all but one had had a recurrence which required further treatment during the first year. Four had been followed for more than two years and two for more than three years, all of whom had required additional treatment. Three cases had 'fairly complete' remissions maintained for a year or more without treatment. Many cases, after a more or less satisfactory remission relapsed and died in spite of further treatment. In the patients who responded favorably, the remissions were quite comparable to those described by Erf et al. The spleen was reduced in size in 23 cases and became no longer palpable in 10.

From the results thus far reported the conclusion seems warranted that P^{32} will bring about a clinical and hematological remission in chronic myelogenous leukemia which is fully equal to that obtained by roentgen radiation and with about the same certainty. It does not cure the disease. It is not yet certain whether the remissions obtained with P^{32} are longer or whether the duration of life is greater, but if there is any difference it is relatively slight. The chief advantage of P^{32} is that it does not cause radiation sickness nor the disagreeable symptoms or toxic manifestations that often accompany the administration of arsenic. In overdosage, however, either in leukemia or in other conditions, P^{32} may cause severe injury to the normal marrow cells, resulting in extreme leukopenia, thrombocytopenia or aplastic anemia.

Since there is a marked individual difference in susceptibility to this drug, great care must be taken in adjusting the dose to the needs of each patient. It has been customary to give 3 to 6 millicuries of radiation in five or six divided doses during the first two weeks and continue at less frequent intervals until a hematological remission is well under way or signs of injury to the marrow appear. Treatment is then stopped, to be resumed only when a relapse begins.

The results reported in cases of lymphatic leukemia are somewhat less favorable. Erf et al.[2] treated 41 cases with P^{32}. No effect was obtained in 16 acute cases (with one exception). Of 25 chronic cases, eight showed

[3] Reinhard, E. H., Moore, C. V., Bierbaum, O. S., and Moore, S.: Radioactive phosphorus as a therapeutic agent. A review of the literature and analysis of the results of treatment of 155 patients with various blood dyscrasias, lymphomas, and other malignant neoplastic diseases, Jr. Lab. and Clin. Med., 1946, xxxi, 107.

a partial and one a complete remission. In these cases there was a substantial reduction in the total leukocyte count, but only a slight alteration in the differential count was observed. There was temporary relief of symptoms, and in most a reduction in the size of the spleen and lymph nodes.

Reinhard et al.[3] reported slightly better results in a series of 45 cases of lymphatic leukemia, 15 acute and 30 chronic. At the time of the report, however, all of the acute cases and 16 of the chronic cases had died. In 20 of 24 cases with a high initial leukocyte count, the latter fell to normal levels, and in 24 of 30 cases the percentage of lymphocytes was more or less reduced. There was relatively little improvement in the anemia. Symptoms were relieved in varying degree, and there was usually some reduction in size of the spleen and lymph nodes. In some cases, however, the latter were little affected, and much greater reduction was secured by local roentgen radiation. The authors concluded that their results were no better than those obtained by roentgen radiation, the chief advantage being freedom from radiation sickness.

Reinhard et al. also obtained no benefit from the administration of P^{32} in cases of monocytic leukemia, lymphosarcoma, Hodgkin's disease, multiple myeloma and in a miscellaneous group having malignant neoplasms of various sorts. In the lymphoblastomata roentgen radiation seems to be much more effective in reducing the size of the lymph nodes than P^{32}, as the latter has heretofore been employed, even though in some cases the dose was large enough to cause serious injury to the marrow.

Cases of polycythemia vera have responded more satisfactorily to radioactive phosphorus. Lawrence[4] in 1940 first reported the successful treatment of two cases. Since then a number of confirmatory reports have appeared, including Erf and Lawrence[5] in 1941 (6 cases), Erf and Jones[6] in 1943 (11 additional cases), and Hall et al.[7] in 1945 (12 cases). More recently Reinhard et al.[3] reported a series of 30 cases treated with P^{32} over a four year period. The results obtained are essentially in agreement and will be summarized as a whole.

Reinhard et al. gave 3.5 to 4 millicuries as a single intravenous injection. If the red blood cell count was over 6 million 90 days later, a second dose of 1 to 3 millicuries was given, and rarely repeated after a second 90 day interval. The total amount needed varied greatly, however, and must be adjusted for each individual patient. No more is given until a relapse occurs.

In most cases there was no appreciable change in the blood until after six

[4] Lawrence, J. H.: Nuclear physics and therapy: Preliminary report on a new method of treatment of leukemia and polycythemia, Radiology, 1940, xxxv, 51.

[5] Erf, L. A., and Lawrence, J. H.: Clinical studies with the aid of radiophosphorus. III. The absorption and distribution of radio-phosphorus in the blood of, its excretion by, and its therapeutic effect on, patients with polycythemia, Ann. Int. Med., 1941, xv, 276.

[6] Erf, L. A., and Jones, H. W.: Radio-phosphorus—an agent for the satisfactory treatment of polycythemia and its associated manifestations; a report of a case of polycythemia secondary possibly to the Banti's syndrome, Ann. Int. Med., 1943, xix, 587.

[7] Hall, B. E., Watkins, C. H., Hargraves, M. M., and Giffin, H. Z.: Radioactive phosphorus in the treatment of polycythemia vera. Results and hematologic complications, Am. Jr. Med. Sci., 1945, ccix, 712.

to eight weeks. There was then a progressive fall in red cell count, hemoglobin and hematocrit reading to normal or subnormal levels. In 11 of 30 cases the count fell below four million cells. The leukocyte and platelet counts also fell, sometimes to subnormal levels. The delayed response is explained by the assumption that P^{32} does not injure the circulating red cells but merely depresses the formation of new cells by the marrow. No fall is to be expected, therefore, until the circulating red cells wear out with age and are removed from the circulation. With the fall in red cell count there was usually substantial subjective improvement although often not complete relief of all the symptoms. The spleen became smaller in virtually all, and could no longer be felt in about two-thirds of the cases. The other objective abnormalities, particularly the red color, also largely disappeared, but hypertension if present was less affected.

The average duration of the remissions has not yet been accurately determined. In Reinhard's series, this varied from five to more than 33 months. In 17 cases the remission had lasted more than nine months; in 11, more than one year; and in five, more than two years, and many were still continuing. In only eight had a second course of treatment been required. In two reported cases [3, 7] following a remission, death occurred with the hematological features of a subacute myelogenous leukemia, an outcome fairly common under previous methods of treatment. A long period of observation will be required to compare the results of treatment with P^{32} with those obtained by other methods, particularly with spray radiation, and to determine to what extent if at all life is prolonged.

The chief drawbacks to the use of P^{32} are the cost and difficulty in obtaining the material; the risk of granulocytopenia and thrombocytopenia if the dose is excessive—which is equally a risk with roentgen radiation; and the slow initial response to treatment. In many patients with excessively high counts and severe symptoms, in whom there is a risk of thromboses, it seems advisable to carry out venesections for temporary relief during the initial period of treatment.

In conclusion, radioactive phosphorus provides a highly effective, convenient form of treatment for polycythemia vera, which is comfortable for the patient and which seems to compare favorably with the procedures commonly used. In chronic leukemia in the earlier stages of the disease it brings about remissions which are similar to those obtained by roentgen radiation, but are not significantly if at all superior. The chief advantage is freedom from radiation sickness. It does not cure the disease, and there is no proof as yet that it prolongs life. It is useless in acute leukemia. In such conditions as Hodgkin's disease, lymphosarcoma and those malignant neoplasms in which its use has been reported, it seems to be much inferior to roentgen radiation. Whenever P^{32} is used, the same precautions to avoid overdosage must be observed as are employed in giving external roentgen radiation.

P. W. C.

REVIEWS

The Eclipse of a Mind. By ALONZO GRAVES. 722 pages; 16 × 24 cm. The Medical Journal Press, New York. 1942.

This autobiography of a newspaper man, diagnosed as manic-depressive, has been carefully edited by one of his attending physicians. The author has been hospitalized several times.

In contrast to the flood of so-called psychiatric novels, this is a work for serious study. It is probably most interesting to psychiatrists, but the sociologist, psychologist or physician concerned with human behavior, its mechanics, motivations and deviations, will find much material worth their attention.

The author is obviously a man of superior intelligence and writing ability. Although his style is often too intricate and his trend of thought at times gets confused, the book is an important and fascinating document. It not only depicts the vicissitudes and failures of a deeply troubled individual as such, but describes aptly the problematical position of a newspaper man in our culture, trying to remain independent and honest in his thinking and reporting, but hitting left and right against political and social prejudices which again and again defeat him. Some of his writing and much of his effort and attitude are reminiscent of Lincoln Steffens, the "muck raker." However, Graves lacks the balance and maturity of Steffens, not having had the benefit either of a secure family background or a thorough and broad education.

As far as the diagnosis of manic-depressive psychosis is concerned, the clinical picture is complicated by many paranoid features. In fact, the author's paranoid trends, of which he is well aware at times, are of paramount importance, in this reviewer's opinion, for a dynamic understanding of the psychotic outbreaks.

The book is well printed. It is highly recommended to serious students of human behavior and motivations.

H. W. L.

The Management of Neurosyphilis. By BERNHARD DATTNER, M.D., Jur.D., Associate Clinical Professor of Neurology, New York University Medical College, with the collaboration of EVAN W. THOMAS, M.D., Associate Professor of Medicine and Assistant Professor of Dermatology and Syphilology, New York University Medical College, and GERTRUDE WEXLER, M.D., Instructor in Dermatology and Syphilology, New York University Medical College. 398 pages; 16 × 23.5 cm. Grune and Stratton, New York. 1944. Price, $5.50.

The authors present in a clear and logical style an adequate discussion of the complex subject of the management of neurosyphilis. The various technics involved are well presented. The text, however, was evidently prepared before the results of the experimental use of penicillin in neurosyphilis were available, so that no estimate of the possible value of this agent is included. The important subject of fever therapy is thoroughly and clearly discussed.

The authors stress the importance of changes in the spinal fluid as a guide in therapy. The technic of spinal and cisternal puncture is graphically described. The use of the Dattner type needle, which has a fine gauge, is advocated, as in the authors' experience its employment reduces the incidence of post-lumbar puncture headaches. The chapter on the examination of the spinal fluid is complete in all details.

H. M. R., Jr.

Cosmetics and Dermatitis. By LOUIS SCHWARTZ, M.D., Medical Director, U. S. Public Health Service, and SAMUEL M. PECK, M.D., Medical Director (R), U. S. Public Health Service. 189 pages with 20 illustrations. Paul B. Hoeber, Inc., New York. 1946. Price, $4.00.

This interesting text contains information of value to both the general practitioner and the dermatologist, although naturally its greatest service will be to the latter. There are formulae of the various type cosmetic preparations on the market presented so that a case of suspected cosmetic dermatitis may be adequately studied by testing with the various ingredients as well as with the whole preparation. Because of its simplicity beauticians may find this book of value. There are brief chapters on anatomy and physiology and an adequate discussion of cutaneous allergy. The pictures are poorly reproduced and might well have been omitted, except for the frontispiece, which is an excellent illustration of dermatitis due to nail polish.

H. M. R., Jr.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Medical Services by Government. By BERNHARD J. STERN, Ph.D., Columbia University. 208 pages; 21.5 × 14 cm. 1946. The Commonwealth Fund, New York. Price, $1.50.

Medical Education and the Changing Order. By RAYMOND B. ALLEN, M.D., Ph.D. 141 pages; 21 × 14 cm. 1946. The Commonwealth Fund, New York. Price, $1.50.

Diagnostic Examination of the Eye. By CONRAD BERENS, M.D., F.A.C.S., and JOSHUA ZUKERMAN, M.D.; F.A.C.S. 711 pages; 24 × 15.5 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, $15.00.

Disorders of the Blood. Fifth Edition. By Sir LIONEL E. H. WHITBY, C.V.O. and C. J. C. BRITTON, M.D., D.P.H. 665 pages; 25 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, $10.00.

The Management of Obesity. By LOUIS PELNER, M.D. 144 pages; 22.5 × 15 cm. 1946. Personal Diet Service, New York.

COLLEGE NEWS NOTES

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Samuel R. Mercer, (Associate), Fort Wayne, Ind.—4 reprints.
Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint.
Gustavus A. Peters, (Associate), Battle Creek, Mich.—11 reprints.
Lawrence E. Putnam, (Associate), Washington, D. C.—2 reprints.
Herbert W. Rathe, F.A.C.P., Waverly, Iowa—2 reprints.
Harold C. Robinson, F.A.C.P., Grand Rapids, Mich.—1 reprint.
Maurice J. Rotkow, (Associate), Des Moines, Iowa—1 reprint.
Howard A. Rusk, F.A.C.P., New York, N. Y.—5 reprints.
Arthur Ruskin, (Associate), Galveston, Tex.—16 reprints.
Oscar A. Sander, F.A.C.P., Milwaukee, Wis.—2 reprints.
Benjamin Saslow, F.A.C.P., Newark, N. J.—1 reprint.
Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—1 reprint.
William Stein, F.A.C.P., New Brunswick, N. J.—1 reprint.
Leon N. Sussman, (Associate), New York, N. Y.—1 reprint.
Morgan Y. Swirsky, (Associate), New Haven, Conn.—1 reprint.
Walter Howard Wilson, (Associate), Raleigh, N. C.—1 reprint.
Edwin E. Ziegler, F.A.C.P., Lancaster, Pa.—1 reprint.

Personnel of the American Board of Internal Medicine

Dr. William A. Werrell, Assistant Secretary-Treasurer of the American Board of Internal Medicine, has recently announced the following personnel of the Board, following elections made in May by the American College of Physicians and in July by the American Medical Association:

James J. Waring, F.A.C.P., Chairman, Denver, Colo.
William S. McCann, F.A.C.P., Vice Chairman, Rochester, N. Y.
Hugh J. Morgan, F.A.C.P., Secretary-Treasurer, Nashville, Tenn.
Marion A. Blankenhorn, F.A.C.P., Cincinnati, Ohio

LeRoy H. Briggs, San Francisco, Calif.
Alexander M. Burgess, F.A.C.P., Providence, R. I.
William B. Porter, F.A.C.P., Richmond, Va.
Burrell O. Raulston, F.A.C.P., Los Angeles, Calif.
Truman G. Schnabel, F.A.C.P., Philadelphia, Pa.
Roy W. Scott, F.A.C.P., Cleveland, Ohio
Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga.
Cecil J. Watson, F.A.C.P., Minneapolis, Minn.

The Board has been increased to 12 members; it previously had nine members. Drs. Burgess, Porter and Scott are new representatives of the College.

Dr. Clarence Orion Cheney, F.A.C.P., White Plains, retired July 1 as Medical Director of the New York Hospital, Westchester Division, a position in which he served for the past ten years. Dr. Cheney previously held similar positions for fourteen years in psychiatric hospitals in New York State. He will continue in his positions as Professor of Clinical Psychiatry at the Cornell University Medical College and consulting psychiatrist to the New York, White Plains, Grasslands and other hospitals. Dr. Cheney will reside at 11 Burling Ave., White Plains, N. Y.

Dr. R. Hugh Wood, F.A.C.P., Atlanta, Ga., has accepted appointment as Dean of Emory University School of Medicine. Dr. Wood succeeds in this position Dr. Eugene A. Stead, Jr., F.A.C.P., who recently became a member of the faculty of the Duke University School of Medicine. Dr. Wood graduated from the Medical College of Virginia, Richmond, in 1921, and has held appointment at Emory University since 1921. He served in the Medical Reserve Corps of the U. S. Army for three years, retiring from it in December, 1945, with the rank of Colonel.

Trudeau Medal Awarded

Dr. Max Pinner, F.A.C.P., Berkeley, Calif., is the recipient for 1946 of the Trudeau Medal of the National Tuberculosis Association. The citation spoke of Dr. Pinner's "curiosity and zeal to attack problems of tuberculosis and related conditions from various angles . . . recognizing that the campaign against the disease proceeds and succeeds only in proportion to its fundamental scientific soundness."

Colonel Rufus Leroy Holt, F.A.C.P., has succeeded Brig. Gen. George R. Callender, F.A.C.P., as Commandant of the Army's Professional Service School.

Secretary of War Robert F. Patterson has announced the appointment of a medical advisory committee, composed of physicians who became familiar with Army medical problems through war-time service, either as officers or civilians, to foster close relations between civilian and Army medicine, and to enable the Army to receive advice on problems of organization and policy from civilian medical leaders. The members of the committee are Dr. Edward D. Churchill, Boston, chairman; Dr. Elliott Cutler, Boston; Dr. Michael DeBakey, New Orleans; Dr. Eli Ginsberg, New York; Dr. William C. Menninger, F.A.C.P., Topeka, Kans.; Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn.; and Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore.

Dr. Arthur M. Master, F.A.C.P., New York, who served from October, 1938, to March, 1946, in the Medical Corps, U. S. Navy, retiring with the rank of Captain, has announced the resumption of the Cardiological Conferences at the Mount Sinai Hospital, New York. The Conferences, which are supervised by Dr. Master and the staff of the Hospital's Cardiology Laboratory, are held at two o'clock on the first and third Tuesday of each month in the Blumenthal Auditorium. Fellows of the College are welcome to attend.

Dr. Francis Bonneau Johnson, F.A.C.P., Charleston, S. C., has resigned from the position of Professor of Clinical Pathology in the Medical College of the State of South Carolina, to which he was appointed in 1918. A graduate of the Medical College in 1908, Dr. Johnson first received appointment to its faculty in 1908 as Assistant in Medicine.

Dr. Edward C. Reifenstein, Jr., F.A.C.P., who has engaged in research work at the Massachusetts General Hospital, Boston, for the past several years has now become Clinical Research Consultant on the staff of Ayerst, McKenna, & Harrison, Ltd. Dr. Reifenstein's office is located at 22 E. 40th St., New York, N. Y.

Dr. Stanton Tice Allison, F.A.C.P., New York, who served in the Medical Corps, U. S. Naval Reserve, from February, 1941, to July, 1946, has been commended by Admiral Halsey for outstanding service. The citation is as follows:

> "For outstanding service as Director of Clinical Services on the U.S.S. BENEVOLENCE when that ship excelled in providing a screening and hospital facility for the care of the 1500 initial Allied Prisoners of War released in the Tokyo Bay area and subsequently as a hospital for the most serious prisoners released from other Japanese prison camps located in approximately two thirds of its main islands. During the three weeks that the U.S.S. BENEVOLENCE was used as the hospital ship for most seriously ill prisoners and throughout which period she cared for many hundreds of patients, only one ex-prisoner died which occurred the day after his admission. To Captain ALLISON belongs much credit for the success and excellence of the treatment administered and for the amazingly low mortality rate. He labored tirelessly and self-sacrificingly, exhibiting unusual energy and initiative. He inspired subordinates when fatigued by his indomitable spirits to renewed efforts. Captain ALLISON's conduct was at all times in keeping with the highest traditions of the United States Naval Service."

Dr. Richard Hale Young, F.A.C.P., on September 15 became Dean of the University of Utah School of Medicine and moved from Evanston, Ill., to Salt Lake City. Dr. Young graduated from the Northwestern University Medical School in 1929, and has since served on its faculty and on the staff of the Evanston Hospital. Dr. Young is a diplomate of the American Board of Internal Medicine.

Dr. Reuben A. MacBrayer, F.A.C.P., retired during July from his work with Ciba Pharmaceutical Products, Inc., of Summit, New Jersey, and is now at home at Southern Pines, North Carolina.

Dr. Thomas Van Orden Urmy, F.A.C.P., formerly of Boston, has accepted the position of Director of Health at Williams College, Williamstown, Mass.

Dr. George G. Burkley, F.A.C.P., Pittsburgh, Pa., who served in the U. S. Naval Reserve from 1941 to early 1946, entered the Medical Corps of the U. S. Navy in August with rank as Captain and is now Chief of Medicine at the U. S. Naval Hospital, Charleston, S. C.

Dr. Thomas Wade Bennett, F.A.C.P., formerly of Columbia, S. C., who served during World War II in the Naval Reserve, has now entered the regular Medical Corps of the Navy with the rank of Commander and is stationed at the U. S. Naval Hospital, Philadelphia.

Col. Henry Clay Michie, F.A.C.P., retired from the Medical Corps of the U. S. Army last February, and is now residing at Alexandria, Va.

Following two years of service in the Medical Corps, U. S. Naval Reserve, from which he retired in April, 1946, with the rank of Commander, Dr. Leon Lewis, F.A.C.P., formerly of New York, has accepted appointment as Associate Professor of Industrial Health in the University of California School of Public Health. Dr. Lewis intends also to engage in private consultation practice in internal medicine, particularly as it concerns the maintenance of health of industrial workers and problems of occupational disease. Dr. Lewis will reside at 133 Ardmore Rd., Berkeley 8, Calif.

Van Meter Prize Award Offered

The Van Meter Prize Award of $300, and two honorable mentions, are offered again by the American Association for the Study of Goiter for the best essays submitted concerning original work on problems related to the thyroid gland. Competing essays may cover clinical or fundamental investigations; should not exceed 3,000 words in length; and should be submitted, in English, not later than January 1, 1947, in typewritten form, double-spaced, to the Association's Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Bldg., Atlanta 3, Ga. The award will be made at the annual meeting of the Association, which will occur in Atlanta, April 3–5, 1947. The essays chosen will be published in the annual Proceedings of the Association; this will not prevent their further publication in any journal selected by the authors.

Dr. Leo Victor Schneider, F.A.C.P., Glenn Dale, Md., has been awarded the Oak Leaf Cluster to the Army Commendation Ribbon for "outstanding and meritorious service" as chief tuberculosis consultant to the U. S. Military Government in Germany. Dr. Schneider served in the Medical Corps, Army of the United States, from October, 1942, to July, 1946, retiring with the rank of Lieutenant Colonel.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., Chairman of the Committee on Nutrition, of the Medical Society of the State of Pennsylvania, presented before a Conference on the Broad Problems of Agriculture, which occurred August 20 at Pennsylvania State College, a paper entitled "Nutrition Problems in Pennsylvania."

Col. Ernest R. Gentry, F.A.C.P., retired from the regular Army Medical Corps on September 30, 1946, and is now located in Baltimore, Md.

The University of Nebraska College of Medicine, Omaha, has announced the establishment of the Dr. Charles Frank Morsman Foundation. The Foundation, supported by a gift of $10,000 from Dr. Charles Frank Morsman, F.A.C.P., Hot Springs, S. D., will devote its efforts to furthering the dissemination of knowledge in the field of endocrinology.

Dr. Irving Sherwood Wright, F.A.C.P., New York, who retired from the Medical Corps, Army of the United States, in February, 1946, with the rank of Colonel, has received the Army Commendation Ribbon, bestowed "for meritorious service as consultant in internal medicine, Office of the Service Command Surgeon, Headquarters, Ninth Service Command."

U. S. P. Board of Trustees Planning Early Publication, U. S. P. XIII

The U. S. P. Board of Trustees met recently at its headquarters in Philadelphia, 4738 Kingsessing Avenue, and laid plans for the publication of the U. S. P. XIII before the end of the current year. Plans are also being made for the development of a comprehensive program upon which to base admissions to the U. S. P. XIV. Consideration is being given to the publication of the Pharmacopoeia in Spanish as well as in English for use in Latin American countries.

Dr. David Walter Gillick, F.A.C.P., formerly of Oklahoma City, has been promoted from District Medical Director to Chief Medical Officer of the Office of Indian Affairs, Department of the Interior, and assumed his new position on July 1 at Talihina Indian Hospital, Talihina, Oklahoma.

Brigadier General George B. Foster, F.A.C.P., was retired from active duty in the U. S. Army on August 31, 1946, and has accepted an appointment as Medical Director of the Cambridge (Mass.) City Hospital.

Col. Cleon J. Gentzkow, (MC), USA, F.A.C.P., has been awarded the Legion of Merit for outstanding service as commanding officer at Deshon General Hospital, Butler, Pa., from October, 1942, to March, 1946. Dr. Gentzkow is now commanding officer of the Valley Forge General Hospital, Phoenixville, Pa.

American Academy of Occupational Medicine

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., has been elected President of the American Academy of Occupational Medicine. The Academy, formed at a meeting in New York in June, has as its aims prevention, diagnosis, treatment and care of occupational illness and injuries; research in pathogenesis of industrial diseases, their prevention and control; improvement in health of industrial workers. Special prerequisites have been established for membership. Drs. E. E. Evans, F.A.C.P., Penns Grove, N. J.; John H. Foulger, F.A.C.P., Wilmington, Del.; and James J. Waring, F.A.C.P., Denver, Colo., were also charter members of the Academy.

The 1947 written examination of the American Board of Internal Medicine will be held on February 17, 1947. The closing date for the acceptance of applications will be November 1, 1946.

Dr. Joseph F. Sadusk, Jr., (Associate), New Haven, Conn., has been awarded the Legion of Merit. The citation states that "Colonel Sadusk made a conspicuous contribution to the expeditious occupation of Japan . . . as preventive medicine officer for the chief surgeon in the advanced echelon of general headquarters in Japan."

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, New York, delivered a paper before the section of Gastro-enterology of the American Medical Association on July 3, entitled "Histamine in the Treatment of Peptic Ulcer" and also had an exhibit on the same subject.

Capt. Walter J. Pennell, F.A.C.P., has retired from the Medical Corps of the regular U. S. Navy, and on September 3, 1946, became the District Health Officer of the Massachusetts Department of Public Health. His office is in Wakefield, Mass.

Dr. Granville L. Jones, (Associate), formerly of Marlboro, New Jersey, has recently accepted appointment as superintendent of the State Hospital, Williamsburg, Va.

Correction

In the August issue of this Journal, page 388, it is recorded that Dr. Nathaniel Uhr (Associate) has been retired from the Army with the rank of Colonel. Dr. Uhr retired with the rank of Lieutenant Colonel. He is now with the Veterans Administration Hospital at Topeka, Kans.

Note to Physicians-Artists

The $34,000 prize contest for physicians' art work on the subject of "Courage and Devotion Beyond the Call of Duty" will be judged at the Atlantic City Centennial Session of the A.M.A. at Atlantic City June 9–13, 1947.

Art works on other subjects may also be submitted for the regular cups and medals.

For full information, write Dr. F. H. Redewill, Secretary, American Physicians Art Association, Flood Building, San Francisco, Calif., or to the sponsor, Mead Johnson & Company, Evansville 21, Ind.

Dr. J. Shirley Sweeney, F.A.C.P., has temporarily discontinued his practice in Dallas, Texas, and his teaching activities at the Baylor University College of Medicine in order to undertake, as Medical Manager, the organization of services in the Veterans Administration Hospital, Fort Logan, Colo.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to September 12, 1946 inclusive).

David I. Abramson, Cincinnati, Ohio (Major, MC, AUS)
Louis K. Alpert, Baltimore, Md. (Major, MC, AUS)

William F. Ashe, Jr., Cincinnati, Ohio (Major, MC, AUS)
Oscar Auerbach, Staten Island, N. Y. (Lt., MC, USNR)

Russell L. Baker, White Salmon, Wash. (Major, MC, AUS)
Ralph G. Ball, Manhattan, Kans. (Col., MC, AUS)
William E. G. Bayley, La Crosse, Wis. (Major, MC, AUS)
Charles A. Breck, Wallingford, Conn. (Major, MC, AUS)

Martin G. Carter, Los Angeles, Calif. (Capt., MC, USNR)
Thomas E. Clark, Columbus, Ohio (Lt., MC, USNR)
James P. Crawford, Del Monte, Calif. (Col., MC, USA)
Robert W. Currie, Billings, Mont. (Major, MC, AUS)

James H. Danglade, Kansas City, Mo. (Comdr., MC, USNR)
Marion T. Davidson, Birmingham, Ala. (Major, MC, AUS)
William C. Dine, Jr., Amarillo, Tex. (Capt., MC, AUS)
Kenneth L. Druet, Salina, Kans. (Lt. Col., MC, AUS)

Daniel B. Faust, Ozark, Ala. (Col., MC, USA)
M. Herbert Fineberg, Boston, Mass. (Col., MC, AUS)
George B. Foster, Jr., Philadelphia, Pa. (Brig. Gen., MC, USA)
Richard France, Baltimore, Md. (Capt., MC, USNR)

Elmer S. Gais, New York, N. Y. (Col., MC, AUS)
Frederick Goldman, Cincinnati, Ohio (Lt., MC, USNR)
Martin G. Goldner, Chicago, Ill. (Capt., MC, AUS)
Seymour J. Gray, Chicago, Ill. (Lt. Comdr., MC, USNR)

George F. Harsh, San Diego, Calif. (Comdr., MC, USNR)
Robert A. Hollands, Pasadena, Calif. (Major, MC, AUS)
John A. Hookey, Sr., Detroit, Mich. (Major, MC, AUS)

Roger H. Keane, Portland, Ore. (Lt. Comdr., MC, USNR)
William E. Kendall, Dwight, Ill. (Col., MC, AUS)
Byrl R. Kirklin, Rochester, Minn. (Col., MC, AUS)
Milton L. Kramer, New York, N. Y. (Lt. Col., MC, AUS)
Victor H. Kugel, New York, N. Y. (Major, MC, AUS)

Howard F. Lawrence, Warren, Pa. (Capt., MC, USN)
John A. Layne, Great Falls, Mont. (Major, MC, AUS)
Byrd S. Leavell, Charlottesville, Va. (Major, MC, AUS)
Isaiah E. Libin, New York, N. Y. (Capt., MC, AUS)
Charles F. Lowry, Kansas City, Mo. (Lt. Col., MC, AUS)

Arthur A. Marlow, La Jolla, Calif. (Col., MC, AUS)
John K. Martin, Seattle, Wash. (Col., MC, AUS)
Alexander McCausland, Blacksburg, Va. (Lt., MC, USNR)
Alphonse McMahon, St. Louis, Mo. (Commodore, MC, USNR)
Perry J. Melnick, Chicago, Ill. (Lt. Col., MC, AUS)
Joseph A. Mendelson, Washington, D. C. (Lt. Col., MC, USA)
M. Hill Metz, Dallas, Tex. (Lt. Comdr., USPHS (R))
Samuel Myerson, New York, N. Y. (Capt., MC, AUS)

Don E. Nolan, Dayton, Ohio (Lt. Col., MC, AUS)
Robert B. Nye, Philadelphia, Pa. (Col., MC, AUS)

Kenneth A. Owen, Akron, Ohio (Major, MC, AUS)

Andrew J. Parker, Pittsburgh, Pa. (Major, MC, AUS)
Walter J. Pennell, Auburn, Maine (Capt., MC, USN)
George P. Perakos, New Britain, Conn. (1st Lt., MC, AUS)

Gilberto S. Pesquera, Mount McGregor, N. Y. (Major, MC, AUS)
Theodore J. Pfeffer, Racine, Wis. (Lt. Col., MC, AUS)

Arthur H. Reynolds, New York, N. Y. (Capt., MC, AUS)
Paul H. Revercomb, Charleston, W. Va. (Lt. Col., MC, AUS)
Monroe J. Romansky, Rochester, N. Y. (Major, MC, AUS)
Leon Rosove, Santa Monica, Calif. (Comdr., MC, USNR)
John J. Rupp, Santa Barbara, Calif. (Capt., MC, USNR)
Henry I. Russek, Brooklyn, N. Y. (Lt. Comdr., USPHS (R))

Earl Saxe, Topeka, Kans. (Lt. Col., MC, AUS)
Nathan Schaffer, East Orange, N. J. (Lt. Col., MC, AUS)
Harry T. A. Seneca, New York, N. Y. (Lt., MC, AUS)
Emil M. Shebesta, Detroit, Mich. (Major, MC, AUS)
Emory L. Shiflett, Louisville, Ky. (Lt. Col., MC, AUS)
Charles L. Spurr, Chicago, Ill. (Lt., MC, USNR)
Robert E. Stone, Chapel Hill, N. C. (Capt., MC, AUS)
Morgan Y. Swirsky, New Haven, Conn. (Capt., MC, AUS)

Ernest M. Tapp, Walla Walla, Wash. (Lt. Col., MC, AUS)
Morris C. Thomas, Indianapolis, Ind. (Col., MC, AUS)
T. Noxon Toomey, Springfield, Ill. (Major, MC, AUS)

Joseph Weinstein, Brooklyn, N. Y. (Lt. Col., MC, AUS)
Francis R. Whitehouse, Rochester, Minn. (Major, MC, AUS)
Udo J. Wile, Ann Arbor, Mich. (Col., USPHS)
John W. Williams, Cambridge, Mass. (Comdr., USPHS (R))

Ellis W. Young, Pittsburgh, Pa. (Capt., MC, AUS)

Solomon L. Zimmerman, Columbia, S. C. (Lt. Col., MC, AUS)

Board of Regents Meet in Philadelphia October 19–20

The Board of Regents of the College held its annual autumn meeting in Philadelphia, October 19–20, and the proceedings will be published in these columns as soon as possible. It is at the autumn meeting that much of the main business of the College is transacted, such as adoption of budget, approval of programs of postgraduate courses, designation of available Fellowships to be awarded election of new Associates and Fellows, etc. It is also anticipated that growing out of the proceedings of this meeting will be an official statement clarifying in greater detail the requirements and criteria of membership.

Omission

In the account of the Forty-Seventh Meeting of the American Gastroenterological Association (College News Notes, August, 1946), the list of participants failed to include Dr. Manfred Kraemer, F.A.C.P., Newark, N. J. Dr. Kraemer presented a paper at the meeting, entitled, "Malnutrition in American Prisoners."

Western New York Members Hold Regional Meeting

Under the Governorship of Dr. Edward C. Reifenstein, Sr., a Regional Meeting of the American College of Physicians was held for members in Western New York, at Syracuse, October 16, 1946. The scientific program was as follows:

1. The Treatment of Empyema of the Pleural Cavity by Penicillin Used Intrapleurally.
   Paul C. Clark, M.D., F.A.C.P., Syracuse.

2. Hiatus Hernia.
   Henry H. Haft, M.D., F.A.C.P., Syracuse.
3. Certain Clinical and Pathological Manifestations of Periarteritis Nodosa.
   J. Winthrop Pennock, M.D., F.A.C.P., Syracuse.
4. Clinical-Pathological Studies of Rheumatic Carditis.
   George H. Reifenstein, M.D., Syracuse.
5. The Renal Mechanisms Involved in Stabilizing the Alkali Reserves of the Body.
   Robert F. Pitts, M.D., New York, N. Y.
6. The Scope of Modern Psychiatry.
   John Romano, M.D., Rochester.
7. Visual Manifestations of Digitalis Poisoning.
   David F. Gillette, M.D., Syracuse.
8. Clinical-Pathological Conference.
   J. Howard Ferguson, Syracuse; Drs. William S. McCann, F.A.C.P., Rochester, and Nelson G. Russell, Sr., F.A.C.P., Buffalo, Discussors.

An evening reception was followed by a dinner at the Onondaga Golf and Country Club, at which Dr. Wardner D. Ayer, F.A.C.P., Syracuse, addressed the group on "Certain Phases of the History of Medicine, Based on the Wolf Portraits, College of Medicine at Syracuse University."

Dr. Richard D. Kepner, F.A.C.P., Honolulu, T. H., has been appointed consultant to the Secretary of War.

Plans Under Way for Twenty-Eighth Annual Session

The plans for the Twenty-Eighth Annual Session of the American College of Physicians, which will be held in Chicago, April 28–May 2, 1947, are now well under way. Dr. LeRoy H. Sloan, General Chairman, is now actively engaged in completing his Roster of Committees, which will include not only the Executive Committee to formulate the planning of the entire program of clinics and panel discussions, but also committees for the individual hospitals which will participate. Dr. Sloan and the members of the committee are most enthusiastic workers. They are determined that this shall be a most rewarding and memorable meeting.

In anticipation of the largest attendance that the College has ever had at an Annual Session, the Palmer House has been selected as headquarters, and arrangements have been made with numerous other hotels in order to reserve the maximum number of rooms that can be procured. A Committee of Physicians, well acquainted with the College Membership, will be named by Dr. Sloan to work in conjunction with the Chicago Convention Bureau on housing arrangements. This Committee will hold weekly conferences in order to make the best possible assignments of rooms to applicants.

Dr. David P. Barr, President, is now making preliminary arrangements concerning subjects and speakers for the Morning Lectures and General Sessions.

Mr. E. R. Loveland, Executive Secretary, is engaged in laying out the floor plans for the Technical Exhibits, in which interest has been shown by a considerable number of outstanding pharmaceutical firms and supply houses, and reports that the business arrangements for the meeting are now well along.

Major General Shelley U. Marietta, (MC), USA, Ret'd., F.A.C.P., Washington, D. C., was elected to the position of President-Elect, and Dr. Louis Mark, F.A.C.P.,

Columbus, Ohio, to that of Second Vice-President, of the American College of Chest Physicians, at the annual meeting of the College which took place at San Francisco in June.

The employes of the San Francisco Department of Public Health recently presented Dr. J. C. Geiger, F.A.C.P., with a beautiful scroll on the occasion of his fifteenth anniversary as Director of Public Health of the City and County of San Francisco. The citation refers to Dr. Geiger's "untiring devotion to duty . . . leadership which has brought international attention to the efficiency and progressiveness of the San Francisco Department of Public Health . . .unusual and continuous personal interest in the employes."

Captain Turville Presents Book, U. S. Naval Mobile Hospital Number Eight, to the College

Captain William H. H. Turville, (MC), USN, F.A.C.P., has presented to the College a copy of the book delineating the development and history of the U. S. Naval Mobile Hospital Number Eight from the time of its commission, on August 12, 1942, until the date of his detachment as Commanding Officer of the hospital, May 17, 1944. The hospital was located on Guadalcanal and the book contains many interesting illustrations and is a most interesting narrative of the organization, building and administration of one of the most important of these novel hospitals. It forms a valuable addition to the College Archives because of the many intimate reports about not only Captain Turville but many other Fellows of the College who were connected with the Hospital.

Dr. Donald T. Chamberlin, F.A.C.P., has now returned to Boston, is limiting his practice to diseases of the digestive system, and has a teaching connection with Harvard University and the Boston City Hospital. He is located at 422 Beacon St.

Dr. Eugene P. Campbell, F.A.C.P., is Chief of the Field Party of the Brazil Division of Health and Sanitation of the Institute of Inter-American Affairs, and is at present stationed at Rio de Janeiro, Brazil. The Cooperative Public Health Program of the Governments of the United States of America and Brazil presented a series of 12 papers before the First Inter-American Medical Congress.

Announcement has been made of the formation of a new committee of the National Research Council which will give advice to the Veterans Administration on medical problems. Dr. O. H. P. Pepper, F.A.C.P., Philadelphia, will act as Chairman of the Committee; its members include the following Fellows of the College: Dr. Hugh J. Morgan, Nashville, Tenn.; Dr. Francis J. Braceland, Rochester, Minn.; Dr. William C. Menninger, Topeka, Kans.; Dr. C. P. Rhoads, New York; and Dr. J. Roscoe Miller, Chicago.

The 98th Annual Meeting of the Medical Society of Virginia was held October 14–16, 1946, at the Cavalier Hotel, Virginia Beach, with Dr. A. Brownley Hodges, F.A.C.P., Norfolk, as Chairman of the Committee on Arrangements. The program of the sessions disclosed the following members of the College to be participants. Dr. Walter B. Martin, F.A.C.P., Norfolk, delivered an address at the Monday evening

session and a paper on "Laboratory and Diagnostic Methods of Interest to the General Practitioner" on Wednesday. Drs. Charles M. Caravati, F.A.C.P., and James M. MacMillan, (Associate), Richmond, presented a paper, entitled, "Gastroscopy: An Aid in the Diagnosis of Occult Hematemesis." Dr. Oscar Swineford, Jr., F.A.C.P., University, was co-author of a paper, "The Coseasonal Treatment of Hay Fever," which was discussed by Dr. J. Warrick Thomas, F.A.C.P., Richmond. Dr. Frank H. Redwood, F.A.C.P., Norfolk, discussed the "Present Status of Shock Therapy," which was presented by Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, co-author. Dr. Paul D. Camp, F.A.C.P., Richmond, was co-author of a report on the subject, "Severe and Fatal Rheumatic Fever with Pancarditis in Virginia." Dr. Julian R. Beckwith, F.A.C.P., Clifton Forge, spoke on "Hypertensive Vascular Disease: Its Evaluation and Management." Participating in a symposium on general practice, Dr. Joseph R. Blalock, F.A.C.P., Marion, presented "Neuropsychiatry as It Relates to the General Practitioner." Dr. George F. Lull, F.A.C.P., Chicago, delivered an address at the Tuesday dinner session.

Dr. Harry W. Shuman, F.A.C.P., Rock Island, Ill., spoke before the Iowa-Illinois Central District Medical Association at Moline, Ill., September 12, 1946, on the subject, "Cardiac and Circulatory Changes in Hyperthyroidism."

Dr. Hobart A. Reimann, F.A.C.P., Professor of Medicine at Jefferson Medical College of Philadelphia, and Dr. William D. Stroud, F.A.C.P., Professor of Cardiology in the University of Pennsylvania Graduate School of Medicine, have been named as two of the 20 members of the National Medical and Scientific Advisory Council of the National Arthritis Research Foundation. This foundation has been organized recently to study the causes, cure and prevention of arthritis and related rheumatic diseases. The American College of Physicians appropriated $1,000 as a donation to the work. A special research center will be established in Hot Springs National Park, Ark.

At a recent meeting to support the Foundation's drive for funds, Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, estimated the cost of medical care of the 3,000,000 persons in the United States who suffer from arthritis and other rheumatic diseases to be of the order of $100,000,000 a year.

Dr. Kern Becomes Professor of Medicine at Temple

Dr. Richard A. Kern, F.A.C.P., Philadelphia, has been appointed to the positions of Professor and Head of the Department of Medicine in the Temple University School of Medicine, and Medical Director of the Temple University Hospital. Dr. Kern succeeds Dr. Charles L. Brown, who recently became Dean of the Hahnemann Medical College and Hospital of Philadelphia.

Dr. Kern is a graduate of the University of Pennsylvania School of Medicine, class of 1914, and has since had a distinguished career in the faculty of that school as well as in the University's Graduate School of Medicine, in each of which he held a Professorship of Clinical Medicine. Dr. Kern served in the Navy Medical Corps in both wars; during World War II, he served as the head of Naval Medical Reserve Specialists Unit No. 9, which staffed the U.S.S. Solace, the only hospital ship in the Pacific during the early part of the war. In 1943 Dr. Kern was assigned to Admiral Halsey's staff in the South Pacific, as Medical Consultant, and, from 1944 to

the end of 1945, he served as Chief of Medicine and Rehabilitation Officer at the U. S. Naval Hospital, Philadelphia, retiring from the Navy with the rank of Commodore. Dr. Kern is presently serving as consultant to the Veterans Administration and as chief of its section for general medicine.

Dr. Anthony Bassler, F.A.C.P., New York, has been elected President of the National Gastroenterological Association, and Drs. Clarence J. Tidmarsh, F.A.C.P., Montreal, and Harry M. Eberhard, (Associate), Philadelphia, have been elected Vice Presidents.

Dr. G. Nelson Furbeck, (Associate), of Mexico City, was released from active duty in the Army last January, and spent the first semester of this year at Tulane University of Louisiana, taking a postgraduate course in tropical medicine. He has now resumed practice at his old location, Gante 1, Mexico, D. F.

While on active duty in the Army, during June, 1945, Dr. Furbeck was awarded the Bronze Star Medal, "for meritorious service in connection with military operations against the enemy at Okinawa Shima, Nansei Shoto, during April, 1945. During an early dawn shelling of the battalion and station by the enemy, Captain Furbeck, the battalion surgeon, was painfully wounded. Within a short period of time the aid station was filled with casualties evacuated from front line units. Disregarding his own wounds, he treated the wounded and arranged for their evacuation, although to do so he was forced to fight down successive waves of nausea caused by his own wounds. He remained on duty all day, steadfastly refusing to be evacuated until relief arrived and another surgeon could take over his duties. His unselfish devotion to duty and to the needs of the wounded was an inspiration to all who saw him in action and was accomplished in the highest traditions of the country he serves." On November 9, 1945, Dr. Furbeck received further official commendation from Col. W. S. Winn, Commanding the Headquarters of the 105th infantry.

Dr. Robin C. Buerki, F.A.C.P., Dean of the Graduate School of Medicine, and Director of Hospitals, of the University of Pennsylvania, Philadelphia, was one of three physicians who received appointment to the Federal Hospital Council. The Surgeon General of the U. S. Public Health Service, Dr. Thomas Parran, F.A.C.P., is *ex officio* Chairman of the Council which will have the responsibility for approving the general regulations for the program of hospital surveys and construction authorized by the Hill-Burton bill.

Dr. Robert J. Mearin, (Associate), New York, was recently commended by Admiral H. K. Hewitt, USN, for his activities as senior medical officer, Advanced Amphibious Training Base, Bizerte, Tunisia, October, 1944, to May, 1945. The citation mentions the following outstanding services: "exceptional professional and administrative ability and energy in supervising medical activities . . . prompt analysis of the problems involved and the initiative which you displayed in instituting control measures completely protected the United States Navy personnel of the . . . Base . . . from this dread disease (bubonic plague) . . . sound judgment and outstanding devotion to duty." Dr. Mearin retired from the Medical Corps, USNR, in May, 1946, with the rank of Lieutenant Commander.

Dr. Samuel A. Levine, F.A.C.P., Boston, delivered the Walter Wile Hamburger Memorial Lecture of the Institute of Medicine of Chicago, October 8, 1946. Dr. Levine's subject was "Treatment of Congestive Heart Failure."

The 96th meeting of the Kentucky State Medical Association occurred September 30–October 3, 1946, at Paducah. The program of speakers included the following:

Dr. Rankin C. Blount, F.A.C.P., Lexington, "Pathogenesis and Treatment of Essential Hypertension."

Dr. Thomas M. Marks, F.A.C.P., Lexington, "What Benefit if Any Does Prostigmine Offer to Cerebral Palsy?"

Dr. William K. Keller, F.A.C.P., Louisville, "Psychiatry for the General Practitioner."

Dr. Samuel A. Overstreet, F.A.C.P., Louisville, "More Stately Mansions."

Dr. Maurice A. Shillington, F.A.C.P., Glendive, has become President of the Montana State Medical Association.

Dr. J. Franklin Waddill, F.A.C.P., Norfolk, Va., has been awarded the Army Commendation Ribbon. The citation states that the award was made for "outstanding and meritorious service as Chief of the Medical Service, Station Hospital, Fort Eustis, Virginia, from September 1942 to June 1944. Colonel (then Lieutenant Colonel) Waddill's administration of the medical service, his teaching program and especially the establishment of a heat disease program helped to maintain a high standard of medical attainment. His persistent adherence to the principles involved in his line of endeavor prevailed to the end that its value to the military service is fully recognized. His efforts have brought great credit to himself, have been of inestimable value to the command and have contributed much to the advancement of medicine in the field of heat disease, meningitis, cardiovascular disease and pneumonia."

Drs. George S. Lull, F.A.C.P., Chicago, and Frank B. Queen, F.A.C.P., Portland, were listed as speakers in the program of the 72nd meeting of the Oregon State Medical Society, which took place at Gearhart, September 26–28, 1946. Dr. Lull's topic was "Activities of Organized Medicine." Dr. Queen discussed "Some Current Problems in Cancer."

The following Fellows of the College participated as speakers at the 105th meeting of the State Medical Society of Wisconsin, Milwaukee, October 7–9, 1946:

Dr. M. Herbert Barker, Chicago, "Infectious Hepatitis."

Dr. Paul D. White, Boston, "The Most Important Therapeutic Measures in the Treatment of Hypertensive Heart Disease."

Dr. Wesley W. Spink, Minneapolis, "Antibiotics."

Dr. J. Arthur Myers, Minneapolis, "The Physician and Tuberculosis."

Dr. Carl V. Moore, St. Louis, "Use of Folic Acid in Treatment of Macrocytic Anemias."

The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York City, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of registration fee. The program has been arranged to cover a wide variety of conditions where allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, prior to November 10.

The A. C. P. Autumn Program of Postgraduate Courses

Four of the College courses on the Autumn, 1946 schedule have now been concluded, namely, No. 1, Internal Medicine, at the University of Pittsburgh; No. 2, Psychosomatic Medicine, at the University of Colorado; No. 3, Internal Medicine, at the University of Oregon; No. 4, Clinical Neurology, at the Jefferson Medical College, Philadelphia.

Courses Nos. 1, 2 and 4 were all oversubscribed. Course No. 3, Internal Medicine, at the University of Oregon, one of the fine courses on the College program, had a relatively small registration because of the lateness in publishing the detailed outline, due to difficulties in the director's office. It is regretted that so fine a course could not have been more widely publicized and taken advantage of by a larger number of College members and other interested physicians.

Course No. 1 deserves special comment. It was given under the direction of Dr. R. R. Snowden, F.A.C.P., during the first two weeks of September. Dr. Snowden was assisted by physicians from virtually every hospital in the Pittsburgh area. A Regional Meeting of the College for Western Pennsylvania was held on September 11, and the program made a part of the course. The Regional Meeting was concluded by a dinner in the evening at the Pittsburgh Athletic Association and was addressed by Dr. George Morris Piersol, Secretary General, and by Dr. Edward L. Bortz, Chairman of the College Committee on Postgraduate Courses, both of Philadelphia. All members of the class and of the faculty were invited as guests to the Regional Meeting. This was the first time the College has given a course in Pittsburgh. A report from the Director indicates his satisfaction with the interest shown by the attending class. The Executive Officers of the College have received several spontaneous letters from physicians who took this course, expressing their appreciation in the highest terms.

The matriculation fees were used to defray local expenses, entertainment, traveling expenses of guest speakers, and for the purchase of a microfilm projector and microfilmed books which were presented to the Presbyterian Hospital where much of the course was conducted. The Presbyterian Hospital will use this apparatus and books for patients who cannot otherwise read, the films being projected on the ceiling above the patient's bed. The gift was made in appreciation for the great efforts put forth by the hospital in making this Postgraduate Course a success.

Courses Yet to Be Concluded

No. 5—Clinical Medicine from the Hematologic Viewpoint, Ohio State University College of Medicine, Columbus, Ohio; Dr. Charles A. Doan, F.A.C.P., Director; October 21–26, 1946.

This course has been registered to its full capacity, 75.

No. 6—Internal Medicine, Gallinger Municipal Hospital, Washington, D. C.; Dr. Wallace M. Yater, F.A.C.P., Director; October 21–November 1, 1946.

This course has a large registration but is not filled to the maximum capacity of 100.

No. 7—Allergy, Roosevelt Hospital, New York, N. Y.; Dr. Robert A. Cooke, F.A.C.P., Director; November 4–9, 1946.

This course has an adequate registration but can still accommodate a few additional registrants.

No. 8—Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease, Massachusetts General Hospital, Boston, Mass.; Dr. Paul D. White, F.A.C.P., Director; November 4–9, 1946.

Although the detailed outline of this course was not published in the Postgraduate Bulletin due to the absence of the Director in Europe, the

course has been oversubscribed by an exceedingly large number. Many of those who cannot be accommodated this year have requested that their names be placed on the waiting list for the next time it is repeated.

No. 9—Gastro-enterology, University of Chicago School of Medicine, Chicago, Ill.; Dr. Walter Lincoln Palmer, F.A.C.P., Director; November 11–15, 1946.
This course has been registered to its capacity of 85.

No. 10—Selected Problems in Internal Medicine, Western Reserve University, Cleveland, Ohio; Dr. Joseph M. Hayman, Jr., F.A.C.P., Director; November 18–23, 1946.
Although this course is new on the College program, it has a very adequate registration. There may be a limited number of vacancies available.

No. 11—Internal Medicine, Royal Victoria Hospital, Montreal, Que.; Dr. J. C. Meakins, F.A.C.P., Director; November 25–December 6, 1946.
It is anticipated that this course will be filled to the capacity of 60, although a few vacancies exist.

No. 12—Bacterial Chemotherapy, Washington University School of Medicine, St. Louis, Mo.; Dr. W. Barry Wood, Jr., F.A.C.P., Director; December 2–7, 1946.
This a limited course, restricted to 20. Twelve have registered at the time of preparation of this report.

No. 13—Cardiology, University of Michigan Medical School, Ann Arbor, Mich.; Dr. Frank N. Wilson, F.A.C.P., Director; December 2–7, 1946.
This course has been greatly oversubscribed but it is hoped that the Director will repeat the course during 1947 and thus accommodate many members who are on the waiting list.

The Spring, 1947 Schedule

In the next issue of this journal we hope to be ready to announce the complete outline of courses to be offered by the College during the winter and spring of 1947. Tentatively under consideration are the following:

ARTHRITIS AND ALLIED CONDITIONS
(Probably at the Mayo Clinic)

CARDIOVASCULAR DISEASE, Dr. Bruce Logue, F.A.C.P., Director
Emory University School of Medicine, Atlanta, Ga., during March

CARDIOVASCULAR DISEASE, Dr. J. Roscoe Miller, F.A.C.P., Director
Northwestern University, Chicago, Ill.; April 21–26, 1947

CARDIOVASCULAR DISEASE, Dr. Thomas M. McMillan, F.A.C.P., Director
Philadelphia General Hospital, Philadelphia, Pa.

CARDIOVASCULAR DISEASE, Dr. Arthur M. Master, F.A.C.P., Director
Mt. Sinai Hospital, New York City

DISEASES OF THE CHEST, Dr. J. Burns Amberson, F.A.C.P., Director
Bellevue Hospital, New York City

GASTRO-ENTEROLOGY, Dr. Henry L. Bockus, F.A.C.P., Director
Graduate Hospital, Philadelphia, Pa.

GENERAL MEDICINE, Dr. James E. Paullin, F.A.C.P., Director
Emory University, Atlanta, Ga.

INTERNAL MEDICINE, WITH EMPHASIS UPON NUTRITION AND METABOLISM, Dr. M. A. Blankenhorn, F.A.C.P., Director
Cincinnati General Hospital, Cincinnati, Ohio

INTERNAL MEDICINE
Massachusetts General Hospital, Boston, Mass.

NEUROPSYCHIATRY, Dr. Hans Reese, F.A.C.P., Director
University of Wisconsin, Madison, Wis.; or Dr. Roland P. Mackay, F.A.C.P., Director
University of Illinois, Chicago, Ill.; or Dr. Edward A. Strecker, F.A.C.P., Director
Institute of the Pennsylvania Hospital, Philadelphia, Pa.

MECHANICS OF DISEASE, Dr. George W. Thorn, F.A.C.P., Director
Peter Bent Brigham Hospital, Boston, Mass.

PERIPHERAL VASCULAR DISEASE, Dr. E. V. Allen, F.A.C.P., Director
Mayo Foundation, Rochester, Minn.

PHYSICAL MEDICINE, Dr. George Morris Piersol, F.A.C.P., Director
University of Pennsylvania, Philadelphia, Pa.

PSYCHOSOMATIC MEDICINE, Dr. Franklin G. Ebaugh, F.A.C.P., Director
University of Colorado, Denver, Colo.

TISSUE GROWTH AND TUMORS, Dr. Stanley Reimann, F.A.C.P., and Dr. E. L. Bortz, F.A.C.P., Directors
Lankenau Hospital, Philadelphia, Pa.

The Advisory Committee on Postgraduate Courses will also consider additional courses in Internal Medicine and other allied specialties. The above suggestions are purely tentative. Watch these columns for developments.

OBITUARIES

DR. EDWARD GODFREY HUBER

Dr. Edward Godfrey Huber, F.A.C.P., Waban, Mass., Professor of Public Health Practice at Harvard University, died July 23, 1946, aged 64 years. He was born in Menomonie, Wisconsin, and spent the greater part of his career in studying and advancing the public health. His experience was a varied one following his graduation from the University of Michigan in 1905. He served with distinction in the Army Medical Corps of the United States from 1908 to 1935, when he retired to devote his entire time to public health. He became Epidemiologist in the Division of Tuberculosis of the Massachusetts Department of Public Health and a member of the Harvard Staff in 1935, and at the time of his death he was Associate Dean of the School of Public Health at Harvard and Professor of Public Health Practice.

Dr. Huber was an efficient organizer and administrator as well as a teacher. He had a keen interest in music, gardening and sports. His passing will be a great loss to his friends and associates and to all those who are concerned with the advancement of public health.

He is survived by his wife, Mrs. Frances Madison Huber and a daughter, Miss Lucille Huber.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. WILLIAM MASTIN SCOTT

Dr. William Mastin Scott, F.A.C.P., Shreveport, Louisiana, died of coronary artery occlusion on July 21, 1946. He is survived by his widow, Mrs. Margaret Sewall Scott; two sons, and three daughters.

Dr. Scott was born in Mobile, Alabama, June 21, 1900. He received his M.D. degree from Tulane University in 1923, and served his interneship at the Highland Sanitarium in Shreveport. Following three years of general practice at Elm Grove, Louisiana, he moved to Shreveport and entered the field of internal medicine. As the years passed he came to occupy a prominent place among the leading internists of Louisiana, and both personally and professionally was held in high regard by his colleagues.

Dr. Scott became an Associate of the College in 1938, and was advanced to Fellowship in 1941. He was a regular attendant at the annual sessions of the College. He was active in the affairs of his Parish and State medical societies, and regularly attended the meetings of the Southern Medical Association, the American Medical Association, and the American Heart Association. A busy practice did not prevent faithful fulfillment of his duties as Visiting Physician to the Shreveport Charity Hospital.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

CAPT. EBEN ELLIOTT SMITH

Capt. Eben Elliott Smith, F.A.C.P., who retired from active service in the regular Navy of the United States on October 18, 1945, died June 16, 1946, after a service in the Navy of 28 years.

Capt. Smith was born in Dillsboro, Indiana, July 12, 1891. He received his B.S. degree from Moores Hill College, and his medical degree from Johns Hopkins University School of Medicine in 1917. He went directly into the Navy following medical school graduation, but at various times pursued postgraduate work at Rockefeller Institute, the U. S. Naval Medical School, the Mayo Clinic and New York Postgraduate Medical School. He had served on the faculty of the U. S. Naval Medical School, as Editor of the U. S. Naval Medical Bulletin and as officer in charge of the Division of Publications of the Bureau of Medicine and Surgery. His various assignments while in the Navy carried him over the world. He had been especially interested in medical editing, aviation medicine and pathology. He had been a Fellow of the American College of Physicians since 1927.

DR. JOHN DANIEL THOMAS

John Daniel Thomas, M.D., F.A.C.P., Washington, D. C., died July 15, 1946.

He was Emeritus Professor of Physical Medicine at Georgetown University School of Medicine and had practiced medicine in Washington for 50 years. He was a Life Member and Past President of the Medical Society of the District of Columbia.

Dr. Thomas was born in Northampton County, Virginia, August 13, 1868. He received his A.B. degree from Hampden-Sydney College in 1889, and his M.D. degree from the University of Virginia in 1892. He served an internship and residency at Gouverneur's Hospital, New York City, 1892–94. He did postgraduate work at the New York Postgraduate Hospital, and in Vienna. He served in the Spanish-American War, and was a Captain in the Medical Corps during World War I. He was on the medical staff of Emergency Hospital and the Washington Home for Incurables, visiting physician at Garfield and Georgetown Hospitals, and consulting physician at Mount Alto Hospital. He had been a consultant in Internal Medicine to the Diagnostic Center of the Veterans Administration, also to the Glenn Dale Sanatorium. He was Professor of Physical Medicine at Georgetown University School of Medicine for many years, becoming Professor Emeritus in 1924.

Dr. Thomas had been very active in the Medical Society of the District of Columbia, was a Fellow of the American Medical Association, a member of the Medical Society of Virginia, the Clinico-Pathological Society and the Metropolitan Club. He had been a Fellow of the American College of Physicians since 1924.

DR. GRANT SAMUEL BARNHART

Dr. Grant Samuel Barnhart, F.A.C.P., Washington, D. C., died recently. He was born in Lock Haven, Pa., September 11, 1868, went to Washington as a young man, receiving his medical degree from the old Columbian University in 1904. He practiced continuously in Washington since that time. For many years he was on the staff of the Washington Tubercular Dispensary. He was a member of the Medical Society of the District of Columbia, a Fellow of the American Medical Association, a Past President of the Washington Medical and Surgical Society, a charter member of the George Washington University Medical Society and the Washington Civitan Club. He had been a Fellow of the American College of Physicians since 1932. He was a 32nd degree Scottish Rite Mason and held many high offices in that organization. He was also affiliated with the Washington Board of Trade, Phi Sigma Kappa Fraternity and the Congressional Country Club.

DR. LOUIS VINCENT McGOVERN

Louis Vincent McGovern, M.D., F.A.C.P., of Brooklyn, N. Y., was born in New York City, November 28, 1874. He received his premedical training at St. Francis Xavier's College, and was graduated from the University of Bellevue Medical College in 1902. Dr. McGovern died in Wyckoff Heights Hospital on April 29, 1946, at the age of 71 of hemiplegia. He was at one time lecturer on Diseases of the Lungs at the Long Island City College of Medicine; former Visiting Physician at St. Catherine's Hospital; also on the staff of Kings County Hospital. He was the author of several published papers, and a Fellow of the American College of Physicians since 1927. He had been certified by the American Board of Internal Medicine and was a member of the Kings County Medical Society.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CLARK ANSON WILCOX

Dr. Clark Anson Wilcox, F.A.C.P., of Wichita Falls, Texas, died on April 4, 1946, of aplastic anemia.

Dr. Wilcox was born in Scottsville, N. Y., February 7, 1890. He received his pre-medical training at the University of Michigan prior to obtaining his medical degree from the New York Medical College and Flower Hospital in New York City, where he graduated in 1916. He then served an internship at the Lying-In and Flower Hospital in New York, later having postgraduate work at Henry Ford Hospital, the Army Medical School, Cornell Medical College and Mayo Clinic. At one time Dr. Wilcox was assistant professor of chemistry and assistant roentgenologist at the New York Homeopathic Medical College. He served from 1920 to 1922 on the

faculty of the Army Medical School and the Army Dental School in Washington, D. C.

During World War I, Dr. Wilcox was commissioned first lieutenant in the Medical Reserve Corps of the U. S. Army, later accepting the commission of captain in the Medical Corps of the U. S. Army, from which he resigned to enter civilian practice in Wichita Falls, Texas. From 1923 until his death, he was radiologist with the Wichita Falls Clinic and Clinic-Hospital. He was a member of the American Medical Association, the Texas State Medical Association and the Wichita County Medical Society and served as vice president of the latter. He was a past president of the Texas Radiological Society. Dr. Wilcox was also a member of the Northwest Texas District Medical Association, the Radiological Society of North America, diplomate of the American Board of Radiology, and Fellow of the American College of Physicians since 1938. He was the author of numerous published papers.

Dr. Wilcox is survived by his widow, two daughters and a grandson. An earnest and conscientious physician, he will be missed by all with whom he came in contact.

M. D. Levy, M.D., F.A.C.P.,
Governor for Texas

DR. BENJAMIN B. FOSTER

Dr. Benjamin B. Foster, F.A.C.P., died at his home in Portland, Maine, on May 8, 1946.

Dr. Foster was born in Portland on October 7, 1881. He attended the local public schools and the Vermont Episcopal Institute. He studied medicine at the Jefferson Medical College at Philadelphia and the College of Physicians and Surgeons at Boston, receiving his medical degree in the latter institution in 1906. He served an interneship at the Boston City and Emergency Hospital and the Vanderbilt Clinic in New York City. He did special postgraduate work at the Vanderbilt Clinic in dermatology and syphilology. Dr. Foster's practice was confined to dermatology. In 1918 he organized the first clinic in Maine for the treatment of syphilis at the Maine Eye and Ear Infirmary; he had direct charge of this clinic until the beginning of his last illness in March of 1945. He was also Chief of the Department of Dermatology and Syphilology at the Maine General Hospital, until his retirement in 1945. For many years he conducted a weekly clinic in Dermatology at the Edward Mason Dispensary.

Dr. Foster became a Fellow of the American College of Physicians in 1930. He was also a member of the Portland Medical Club, the Cumberland County Medical Society, the Maine Medical Association, the Aegis Club, the Alpha Kappa Kappa Fraternity, and the New England Dermatological Society.

E. H. Drake, M.D., F.A.C.P.,
Governor for Maine

DR. LEON JUDAH SOLWAY

Dr. Leon Judah Solway, M.D., F.A.C.P., Toronto, Ontario, died December 14, 1945, his death not having been reported to the College until September, 1946.

Dr. Solway was born in Russia in 1885. He received his B.A. degree from the University of Toronto in 1907, and his M.B. degree from the same institution in 1909. He did postgraduate work in London, England, and had practiced for many years in Ontario. He was at one time assistant in Medicine at the University of Toronto, and on the staff of the Toronto General and the Toronto Western Hospitals. For the last several years he had been physician-in-chief, Mount Sinai Hospital.

Dr. Solway was a diplomate of the American Board of Internal Medicine, a member of the Toronto Academy of Medicine, the Ontario Medical Association, the Canadian Medical Association, and the American Heart Association. He had been a Fellow of the American College of Physicians since 1939, and a member of the Royal College of Physicians of London since 1922.

DR. WARD J. MACNEAL

Born at Fulton, Michigan, February 17, 1881; died in New York City, August 16, 1946.

Thursday, August 16, began as all days began for Dr. MacNeal within recent years. After breakfast he walked slowly to the Hospital. Having arrived at the laboratory, he gave his first attention to the routine work of the Hospital, saw some patients on the wards and on the private corridor who suffered from endocarditis or blood stream infections, reviewed the progress of the research on rheumatic fever that had arrived at a satisfactory conclusion, and finally dictated and signed a number of letters. It had been a pleasant and profitable morning's work, for the research on rheumatic fever after many years of discouragement at long last was drawing to a close in a highly satisfactory manner.

Leaving word that he would return at two o'clock, he walked home for lunch and his customary rest period. His wife had an unimportant social engagement and left happily to keep it as soon as the meal was completed. Soon after 2:00 p.m. the laboratory staff became worried at his failure to keep his appointment and after a suitable interval sent a messenger to his apartment. With the help of the house superintendent an entrance was effected. Dr. MacNeal had quietly died in his sleep. And so came to an end a typical day which was crowded with useful work and which might well be cited as typifying all the days of his adult life.

In December, 1918, Dr. MacNeal returned from nearly two years of service overseas with the United States Army in France to find his oldest son dying of bacterial endocarditis. It would appear that he made a pledge to himself to find at least some of the answers to the problem of bacterial

endocarditis and rheumatic fever. He made many and various approaches to these problems through succeeding years; the answer to bacterial endocarditis was successfully completed in the late thirties. It was not, however, until May of 1946 that he was able to announce the isolation of a virus from the blood stream of a child suffering from acute rheumatic fever that was capable of producing non-bacterial endocarditis in inoculated animals. This finding was duplicated in the following months in a number of cases of rheumatic fever. Personally he was wholly convinced that he had isolated the etiological factor causing rheumatic fever. It should be added, however, that Dr. MacNeal fully recognized the fact that there was still much work to be completed before the proof was all in hand for a positive announcement. Nevertheless it seems probable that his main task was completed except for the final publication which, after all, could be safely left in other hands, and so, having kept faith with his son, he quietly died.

Dr. MacNeal received his A.B. degree from the University of Michigan in 1901, his Ph.D. degree in 1904, his M.D. degree in 1905; in 1939 the University awarded him the honorary degree of Doctor of Science. He served as Fellow and instructor in bacteriology and histology at the University of Michigan (1901–06), instructor in anatomy and bacteriology at the University of West Virginia (1906–07), assistant professor of bacteriology at the University of Illinois (1907–11), and finally in 1912 became professor of pathology and bacteriology at the New York Post-Graduate Medical School and Hospital—a post he held for thirty-four years. For a time he was the medical adviser to the Josiah Macy Jr. Foundation. In the first World War he was on active duty in France, entering the Medical Corp as a Captain and receiving promotion to Major. His war service included a tour of duty with the American Trench Fever Commission, and he was for more than a year in command of the Central Laboratory at Dijon. His interest continued after the war, and he attained the rank of Colonel in the Medical Reserve Corp. It was only factors of personal health that kept him from active service in the second World War.

During his thirty-five years of active service at the New York Post-Graduate Medical School and Hospital, he served on the Board of Directors for three years (1921–24) and was vice chairman of the Medical Board for a number of years. His main task, however, at the Hospital was to find time outside routine duties to do research work. This meant a careful budgeting of his time and a complete lack of holidays or periods of relaxation. He did find time to do much of the investigation and the editorial work of the Thompson Pellagra Commission. The histological structure of the spleen engaged his interest, and the resulting publications became authoritative. Bacteriophages in his skilled hands became an effective agent before the days of the sulfa drugs and a valuable adjunct in treatment after their introduction. However, the problems of bacterial endocarditis and rheumatic fever were his chief recurring interests and will perhaps bring to his name enduring fame.

Dr. MacNeal was the author of "Studies in Nutrition" and the editor of the second edition of "Microörganisms." He was a valued member of many medical societies—his County, State and national associations, American College of Chest Physicians, New York Pathological Society, New York Academy of Medicine, Society of Experimental Biology and Medicine, Society of American Bacteriologists, American Society for Cancer Research and the American Association of Pathology and Bacteriology. He was a diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1924. He had served as president of the New York Pathological Society and of the American Association for Cancer Research.

It can be written of Dr. MacNeal that honorary distinctions had for him little meaning unless they could be made to serve a useful and enlightening purpose. His outspoken honesty of opinion and his sense of duty were sometimes painful, if admirable, virtues to those who loved him most. He was a loyal friend and only with the greatest reluctance believed ill of those to whom he had once given his trust and confidence. He had a fine sense of humor, though it is to be feared that too few took time to find it out. His feeling of the importance of the job of living and a lack of convivial habits did not contribute to an easy acquaintance or set the stage for a passing moment of good fellowship. Probably the most satisfying moment in his life was that when he was able to assure himself with certainty that he had driven an entering wedge into the obscure story of rheumatic fever. The essentials of a task, set many years earlier, completed, it was not only typical but fitting that he should lay aside the burden of life. Those of us who knew Ward MacNeal best can hardly envisage him without an honest job on his mind and heart.

MARSHALL CARLETON PEASE, M.D., F.A.C.P.

DR. HYMAN I. SPECTOR

Hyman I. Spector, born July 15, 1894; died July 6, 1946. Associate Professor of Medicine, St. Louis University School of Medicine. Fellow of the American College of Physicians since 1938.

The death of Dr. Spector brought to a close an unusually useful life. Dr. Spector, during the course of twenty years, had taught many students who remember him with gratitude and who mourn his passing. He was exceptionally well endowed as a teacher, was devoted to his duties and displayed a background of high character which everyone felt and appreciated.

In his particular field of diseases of the chest, he attained national prominence. He published actively and was a zealous worker for the special organizations in his field. He was one of those teachers it is unusual to have in a medical school, but above all he was a sincere, honest and devoted Doctor.

Among the positions he held were: Past president, Mississippi Valley Conference on Tuberculosis; formerly vice president, St. Louis Tuberculosis Society, and chairman of the Committee on Industrial Health of the Missouri State Medical Association; chief, medical section, St. Louis Health Department from 1934 to 1943; at various times affiliated with Firmin Desloge Hospital, Mount St. Rose Tuberculosis Sanatorium, St. Mary's Hospital Koch Hospital, Jewish Hospital, and chest consultant, U. S. Marine Hospital, Kirkwood, Mo.; Fellow and former Regent, American College of Chest Physicians; member, Trudeau Society, American Public Health Association, and others; author of several published papers.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri.

DR. ISAAC HALL MANNING

Dr. Isaac Hall Manning, F.A.C.P., of Chapel Hill, North Carolina, was born in Pittsboro, North Carolina, September 14, 1866. He obtained his pre-medical training at the University of North Carolina; graduated in medicine from the Long Island College Hospital, Brooklyn, N. Y., 1897. He did postgraduate work at the University of Chicago and at Harvard Medical School.

Dr. Manning was Professor of Physiology at the University of North Carolina from 1901 to 1939. He was Dean of the School of Medicine from 1905 to 1933. He was Professor Emeritus of Physiology from 1939 to 1946.

Dr. Manning had been President of the Medical Society of North Carolina in 1933, President of the Hospital Savings Association of North Carolina, from the time of its organization in 1935 until 1942, when he became Chairman of the Board of Medical Directors. He was a member of the American Medical Association, a Fellow of the American College of Physicians since 1930. In 1940 the Alumni Association of the University of North Carolina School of Medicine honored him by presenting a portrait of him to the University. He died on February 12, 1946.

DR. ALANSON FILER BORT MORRIS

Dr. Alanson Filer Bort Morris, of Pittsburgh, Pa., an Associate of the College, died on February 6, 1946, in St. Stephen's School. Dr. Morris was an Associate of the College by virtue of membership in the old American Congress on Internal Medicine, which was merged with the College in 1926. He was born in 1868 and received his medical degree from the University of Pittsburgh School of Medicine in 1896. He served during World War I in the Medical Corps of the U. S. Army and was a Lieutenant Colonel in the Medical Reserve Corps thereafter. At one time he was first Vice President of the Allegheny County Medical Society. His death was due to coronary occlusion.